Review

“Genomic Insights into Knobloch Syndrome: A Meta-Analytical Perspective”

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"Genomic Insights into Knobloch Syndrome: A Meta-Analytical Perspective"

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Abstract: A rare genetic disorder caused by col18.a1 mutations, inherited mostly in autosomal recessive and rarely in autosomal dominant pattern, giving rise to ocular abnormalities and other associated disorders, the condition is referred to as Knobloch syndrome. This paper overviews the anterior and posterior ocular symptoms in Knobloch patients, thus demonstrating the major findings in Knobloch cases including the mutational analysis which discusses the proteins involved and exon number on which mutations are detected. Animal modeling done by knocking out col18.a1 has also been discussed to determine the functions of this gene which have been identified based on anomalies found in knock-out mice.

Keywords: Mutation; Col18A1; Knobloch syndrome; mouse modeling; treatments

Introduction

Knobloch syndrome is an autosomal recessive disorder characterized by abnormalities most commonly in ophthalmic regions. The most common symptoms of Knobloch syndrome include retinal detachment, occipital encephaloceles, and high myopia (1). Apart from ocular and occipital skull abnormalities, Knobloch syndrome can give a range of phenotypic discoveries like lung hypoplasia, hyperextensible joints, duplication of the renal collecting system, epilepsy, neuronal migration abnormalities, and dysmorphic findings such as midface hypoplasia, high-arched palate, micrognathia, flat nasal bridge, and dental abnormalities (4). It is a genetic disorder that is caused by mutations in the gene Col18A1 and is inherited in an autosomal recessive pattern. This condition is acquired in an autosomal latent example, which implies that mutations have occurred in both duplicates and copies of every cell's gene. One copy of a mutated gene will be present in both parents of the person with an autosomal recessive condition means the parents are a carrier, however, they commonly don't give indications and manifestations of their condition. This syndrome is named after one of the two authors named W.H Knobloch who first reported this disease along with his companion in a family where five out of ten siblings were affected. Their parents had a non-consanguineous marriage. To date, three types of Knobloch syndromes have been reported. Type 1 is because of mutations in the col18A1 gene however the causative genes for type 2 and 3 have still not been identified. Influenced people may likewise have irregularities in the focal space of the retina, called the macula. The macula is accountable for sharp focal vision, which is required for point-by-point errands like perusing, driving, and perceiving faces. Because of irregularities in the retina, vitreous, and macula, individuals with Knobloch syndrome can raise visual deficiency or blindness in one or both eyes. Knobloch syndrome occurs due to biallelic mutations in Col18A1 (2). Col18A1 is associated with Knobloch syndrome. Collagen XVIII is a non-fibril-framing. It is more like a short isoform communicated in epithelial and endothelial base layers all through the body however especially in the eye, where it plays a significant formative part (3). Knobloch disorder is an uncommon condition. Although, the specific prevalence of the condition is obscure. The countries from where Knobloch cases were reported; are shown by red dots in the map given below.

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SYSTEMATIC ANALYSIS OF SYMPTOMS

Table 1 shows the data of case reports of Knobloch patients reported to date. The symptoms are divided based on an anterior and posterior division of the eye and other clinical observations and associations found in those patients such as skeletal abnormalities, facial dysmorphisms, neurological disorders, and other interlinked malformations. Each row individually represents the records of a single research publication and includes all the cases discussed in that paper.

Table 1.

Sr. no	Refrences	No of Patients	Age	Ethnicity	Anterior Symptoms	Posterior Symptoms	Associations	Journals	Journals' Country	
1	Czeizel et al 1992	2	6-14 years	hungarian family	blurred vision, enlarged	macular atrophy, high	occipital bone abnormality,	*American journal of medical*	United States	
2	Seaver et al 1993	2	11 y, 2 y		posterior perinuclear lens	severe retinal pigment	occipital bone abnormality,	*American journal of medical*	United States	
3	Bueno et al 1994	11 Cases	24 y, 18y, 31y		blurred vision, lens	retinal detachment, retinal	polymicrogyria, occipital bone	*American journal of medical*	United States	
4	Sertie et al 1996	11 cases		Brazilian family	iris transillu	macular atrophy, high	Encephalocele	*Human molecular genetics*	United Kingdom	

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5	Wilson et al 1998	2 cases	9 months, 1 month	Caucasion family	nystagmus, perinuclear lens opacity	high myopia, retinal detachment, retinal	Encephalocele, unusual pulmonary lymphatic condition,	*American journal of medical genetics*	United States
6	Sertie et al 2000	24 cases		Brazilian family	lens subluxation, corneal	high myopia, retinal degeneratio	chronic cardiac hypertension, facial	*Human molecular genetics*	United Kingdom
7	Suzuki et al 2002	14 cases	3 days - 33 yrs	Brazilian, North American, Canadian-	Blurred vision	myopia, retinal degeneration, retinal	Epilepsy, Encephalocele, occipital scalp defects, ocular	*American journal of human genetics*	United States
8	Kleimann et al 2003	4 cases	11y, 7y, 19y,13y		exotropia, nystagmus, esotropia	retinal pigment epithelial atrophy, high	epilepsy, mental delay, pleural thickening ventricular	*American journal of medical genetics*	United States
9	Sarra et al 2003	4 cases		Eastern Switzerland		Retinal pigment epithelium atrophy, retinal		*Archives of ophthalmology*	United States
10	Menzel et al 2004	4 cases		Hungarian and New Zealand families	Lens abnormalities, no light percepti	atrophy, high myopia cataract, retinal detachment,	Encephalocele, mental delay, meningocele, unusual	*Human mutation*	United States
11	Duh et al 2004	1 case	16 months	American Indian, African American	hypoplastic iris crypts, bilateral leukocori	cataract, tasellated fundus, retinal	occipital scalp defects, crow's feet,	*Ophthalmology*	United States
12	Keren et al 2007	2 cases	2 years	Algerian family	nystagmus, loss of vision	high myopia, retinal detachment, peripheral	Encephalocele, neurodevelopmental disorders,	*American journal of medical genetics*	United States
13	Khaliq et al 2007	5 cases	18y, 10 y, 16y, 15y, 9y	Pakistani Family	nystagmus, optical phthisis, night	high myopia, retinal degeneration, macular	Occipital focal skin defect, swolen purplish hairless patch	*American journal of medical genetics*	United States
14	Connell et al 2008	1 case	8 y			clumps in retina	vomiting, pyloric stenosis, nodular leisions,	*International journal of paediatric dentistry*	United Kingdom

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15	Theresa et al 2008	1 case	7 y			high myopia, peripheral retinopathy	language difficulties, biventricular hypertrophy, dolichocephalic skull with micrognathia,	*Ophthalmic genetics*	United Kingdom
16	Suzuki et al 2009	5 cases	1 y	Brazilian and North American families	Blindness	high myopia, enophthalmos, myopic degeneration, myopic astigmatism	Encephalocele	*Molecular vision*	United States
17	Mahajan et al 2010	3 cases	4y, 7y, 11y	Al Saluadorian family	blurred vision, nystagmus	high myopia	neurodevelopmental disorders, encephalocele, alopecia in occipital region,	*American journal of medical genetics*	United States
18	Bongiovanni et al 2011	1 case	12 y	Caucasion family	exotropia, porterior perinuclear lens opacity, lens dislocation, loss of	Fetal vasculature, macular scarring, viterous detachment, glaucomatous		*Clinical ophthalmology*	New Zealand
19	Aldahmesh et al 2011	13 cases	12y, 15y, 21y, 8y, 7y, 4y, 5y, 14m	Saudi origin families	ectopia lentis, lens subluxation	high myopia, retinal degeneration, cataract, retinal detachment, optical phthisis,	mental delay, occipital bone abnormality, occipital cutis aplasia, right clavicular pseudoarthrosis	*Journal of medical genetics*	United Kingdom
20	Khan et al 2012	8 cases	4y-15y	Saudi origin families	Blurred vision, exotropia, nystagmus, esotropia, porterior perinuclear lens opacity, scattered	severe retinal pigment epithelial atrophy, high myopia,characteristic vitreo-retinal degeneration, ondensations	epilepsy, mental delay, encephalocele, focal hair defect, occipital focal skin defect	*The British journal of ophthalmology*	United Kingdom

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21	Meier 2013	1 case	7y			retinal detachment, abnormal vitreous,		*e Monatsb latter fur*	Germany		
22	Peluso et al 2013	1 case	30y	Southern Italy	Blurred vision, exotropia, nystagmus, loss of vision, hypermetrophic refraction,	retinal dystrophy, night blindness	mental delay, cognitive delay, autistic disorder	*Orphanet journal of rare diseases ,*	United Kingdom		
23	Khan et al 2013	1 case	3y	Saudi Arabian	Blurred vision, nystagmus, microphthalmia , lens subluxation,	retinal atrophy		*Ophthalmic genetics*	United Kingdom		
24	Haghighi et al 2014	10 cases		Iranian ancestry	Blurred vision, esotropia, nystagmus, porterior perinuclear lens opacity,	macular punched out lesions, high myopia, characteristic vitreo-retinal		*PloS one*	United States		
25	Ahmet et al 2014	4 cases	13y-22y	Turkish Family	loss of vision, lens subluxation, congenital aphakia, leukoma	characteristic vitreo-retinal degeneration, retinal	encephalocele, polymicrogyria, occipital bone abnormality, facial dysmorphisms,	*Pediatric neurology*	United States		
26	Khan et al 2015	1 case	3y	Saudi Arabian	nystagmus, microphthalmia , lens subluxation,	nerve, mild cone-rod dystrophy, retinal atrophy	occipita lobe defects, occipital bone abnormlity	*Ophthalmic Genetics*	United Kingdom		
27	Albakri et al 2016	7 cases	6y-17y		Blurred vision, lens subluxation,	retinal pigment epithelial atrophy, macular punched out lesions, high	occipital scalp defects	*Ophthalmic Genetics*	United Kingdom		
28	Hull et al 2016	12 cases-7 families	2y-38y	Indian/British/Slovak/Arab/Northern Europea	Blurred vision, nystagmus, posterior perinuclear lens opacity, iris transilluminatio	severe retinal pigment epithelial atrophy, macular	Epilepsy, mental delay, encephalocele, polymicrogyria, alopecia in occipital	*JAMA ophthalmology,*	United States		

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29	Charsar et al 2017	2 cases	29 m		Nystagmus, esotropia, bilateral buphthalmos, amblyopia,	High myopia	Epilepsy, mental delay, polymicrogyria, seizures, brainstem volume loss	*Pediatric neurology*	United States
30	Ebrahim et al 2017	1 case	7y	Afghani	Nystagmus, anterior chamber parenthesis	pigment epithelial atrophy, high myopia, characteristic	polymicrogyria, seizures	*Digital journal of ophthalmology*	United States
31	Gradstein et al 2017	1 case	2m		Blurred vision, nystagmus, esotropia	atrophy, high myopia, retinal detachment, retinal	Polymicrogyria, cognitive delay, seizures,	*Documenta ophthalmologica. Advances*	Netherlands
32	Corbett et al 2017	4 cases	41y-59y	Northern-European descent, born in Australia	Blurred vision, nystagmus, ectopia lentis, optical phthisis,	High myopia, white cataract, retinal detachment, optic atrophy, fundus	Polymicrogyria, mental delay, learning and language difficulties,	*European journal of medical genetics*	France
33	White et al 2017	2 cases	7m, 13y		Blurred vision, exotropia, nystagmus, esotropia,	pigment epithelial atrophy, high myopia, macular atrophy,	Mental delay, polymicrogyria, grey matter thickening in gyri,	*BMC ophthalmology*	United Kingdom
34	Beshri et al 2018	1 case	2m		Bilateral buphthalmos, no light perception, epiphora	High myopia, retinal detachment, elevation of optic disc, peripheral vitreoretinopathy, retinal	Occipital bone abnormality, hypotoxia	*Middle East African journal of ophthalmology*	India
35	Zhang et al 2018	3 cases	31y, 33y, demised	Chinese Family	Blurred vision, exoptropia, loss of vision, lens subluxation,	High myopia, retinal detachment, white cataract, vitreous detachment, macular scarring,	Epilepsy, frontal cortical dysplasia, cerebellar malformations	*International journal of ophthalmology*	China
36	Suri et al 2018	10 cases	41y-69y		Neovascular glaucoma	Tilted optic nerve, retinal atrophy	premature arterial contractions	*Human molecular genetics*	United Kingdom

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37	Khan et al 2018	5 cases	20m-16y	Emirati family	Nystagmus, esotropia, optial phthisis, hyperteloris	Macular atrophy, high myopia, white cataract, retinal detachment,	Mental delay, occipital tissue swelling, occipital lobe defects, partially deaf,	*Ophthalmic genetics*	United Kingdom
38	Alsulaiman et al 2019	5 cases	2m-5y		Blurred vision, nystagmus	Macular punched out lesions, retinal detachment, retinal staphylomas,	Occipital lobe defects,	*Ophthalmology*	United States
39	Thau et al 2019	5 cases			Blurred vision, nystagmus, ectopia lentis, convergent strabismus,	severe retinal pigment epithelial atrophy, high myopia, tessellated fundus, retinal	Alopecia in occipital region, occipital dermal sinus tract, occipital scalp defects, skull abnormalities,	*Ophthalmic surgery, lasers & imaging retina*	United States
40	Mayer et al 2020	20 cases		Arab villages of Israel and the	Blurred vision, nystagmus, microphthalmia, anterior	White cataract, retinitis pigmentosa, night blindness, foveal hypoplasia,	Opthalmic disorder, photophobia, mental delay, osteopetrosis, Usher syndrome,	*European journal of human genetics*	United Kingdom
41	Balikova et al 2020	3 cases	2y,15y,46y		Blurred vision, nystagmus, lens dislocation, hypoplastic iris crypts, iris transillumination, correctopia, up-slanting palpebral fissures,	severe retinal pigment epithelial atrophy, high myopia, macular atrophy, macular punched out lesions, retinal detachment, retinal thinning, fundus atrophic lesions, abnormal vitreous,	occipital focal skin defects, occipital bone abnormality, alopecia in occipital region, bilateral renal atrophy, chronic cardiac hypertension, dislipidemia, sleep apnoea, accessory spleen, venous insufficiency in lower limbs, atrophic skin	*Ophthalmic genetics*	United Kingdom
42	Capurro et al 2020	1 case	8y	Chile	Blurred vision, nystagmus, aphakic dilated left pupil, iris transillumination, bilateral buphthalmo	high myopia, irregular choriocapillaris, abnormal vitreous, loss of neuroretinal rim in temporal optic disc,	Alopecia in occipital region, facial dysmorphism, short neck and low set of ears	*American journal of medical genetics*	United States

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43	Levinger et al 2020	4 cases	1y, 3.5y, 22y, 26y	Jewish, Muslim Arab,	Nystagmus, iris transilluminati on, optical phthisis,	high myopia, retinal detachment, mild cone-rod dystrophy, albinotic retina, scarring of retina, retinitis pigmentosa,	Epilepsy, polymicrogyri a, alopecia in occipital region, albinism, Dandy walker malformation s,	*European journal of ophthalmo logy*	Italy
44	Marzo et al 2021	1 case			Posterior perinuclear lens opacity, aphakic dilated left pupil, featureless iris	High myopia, fundus atrophic lesion, hypopigmented fundus, macular hypoplasia, absence of choriocapillaris, retinoschisis,	Encephalocel e, occipital focal skin defects	*Canadian journal of ophthalmo logy(Journal canadien d'ophtalm ologie)*	United States
45	Wang et al 2021	6 cases	4m-5y	Chines e Familie s	Convergent strabismus, loss of vision	High myopia, white cataract, tessellated fundus, mild cone-rod dystrophy, foveal hypoplasia, choroidal sclerosis,	Mental delay, alopecia in occipital region, occipital scalp defects, skull abnormalities , cerebellar malformation s, ataxia,	*Frontiers in cell and developme ntal biology*	Switzerla nd
46	Antonar kis et al 2021	2 cases	24y, 26y	New Zealan d family	No light perception	vitreo-retinal degeneration, abnormal vitreous, flat retina, white cataract, retinal detachment, retinal nodular opacities	Encephalocel e, learning and language difficulties, hairless scalp with one tuft, autistic disorder	*Human molecular genetics*	United Kingdom
47	Wawrzy nski et al 2021	2 cases	27y, 29y		Blurred vision, optical phthisis, pupillary dilation, no light perception, corneal edema,	High myopia, retinal detachment, retinal staphylomas, retinal pigmentosa, retinal dystrophy,	Epilepsy, occipital bone abnormality, learning and language difficulties, nausea	*Journal of glaucoma*	United States
48	Venkate shappa et al 2021	1 case	7y			High myopia, retinal detachment, white cataract	Encephalocel e, polymicrogyri a, occipital bone	*Pediatric neurosurg ery*	Switzerla nd

Causes

Mutations in COL18.A1 are the novel cause of this syndrome. This gene plays its role in the building of collagen XVIII which is an important structural protein found in the body's connective tissues. Collagen produces endostatin, endostatin is a signaling molecule and it retards the proliferation and migration of endothelial cells. (5) Presence of collagen in appropriate amounts is

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very significant for normal eye development. 21q22.3 was the very first locus identified for Knobloch syndrome in 1996 in 11 affected people in a Brazilian family by sertie et al. (6) Recently mutations in another gene have been identified in Knobloch type 2 patients which is PAK 2 in two affected siblings with unaffected parents. They confirmed the mutant variant in affected children with the help of Sanger sequencing. PAK2 gene plays its role in cell growth, survival, and migration (7). Homology modeling of the PAK 2 gene showed that Glu435, Ser371, and Trp409 are present in the catalytic active site of the gene. These residues are significant for the correct conformation and stability of helical structures. A point mutation in (Glu435Lys) which is present at the active region domain of the PAK2 gene seems important for the kinase activity of the gene because this mutation has led to a decrease in phosphorylation at the catalytic site (8). Nonfunctional or haploinsufficiency of the PAK2 gene has resulted in patients with autism-related behaviors, cytoskeleton impairment, dysplasia+, bifid thumb growth delay, and related neurological disorders (9)(10)(11). All these clinical findings are also seen in patients with Knobloch syndrome having mutational COL18.A1 gene which provides clear evidence of a strong association between the two genes. Antonarakis et al hypothesized that some functional correlation might exist between COL18.A1 and PAK2 because both work in association with integrins and are activated by RAC1 which is involved in the regulation of many cell processes in the body (8).

SYSTEMATIC ANALYSIS OF MUTATIONS

Following is the table designed by analyzing the previously present data about the mutations reported in patients of Knobloch syndrome:

Table 2 discusses the type of mutations identified after genome sequencing of Knobloch patients. A total of 65 mutations have been reported in Col18.a1 and PAK2 gene, being a cause of Knobloch syndrome. Out of which, 28 were deletions, 6 were insertions, 5 were duplications and 26 were substitutions. Within the insertion and deletions, 28 were frameshift.

Table 2.

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Mutation NM_03	Protein	Exon number of 43	Types of Mutation
In 5' UTR (-50,112 nucleotides)		1	
c.895delG	p.Val299Serfs*5	4	Deletion, Frameshift
c.1469-2A>G		7	Substitution
c.1604insC	p.Gly538Argfs*55	9	Insertion, Frameshift
c.1761_2054del	p.Asp589_Gly686del	9-14	Deletion
c.1778-9insA	p.Asp593Glufs*58	10	Insertion, Frameshift
c.2325_2326delCCinsA	p.Pro777Leufs*127	17	Deletion, Insertion, Frameshift
c.2416C>T	p.Arg806*	18	substitution
c.2437-2A>G; c.3213dupC		17??	substitution, duplication
c.2645delT	p.Leu882Profs*22	23	Deletion, Frameshift
c.2658dupC	p.Gly887Argfs*23	23	Duplication, Frameshift
:c.2970_2971delAGinsC			Deletion, Insertion
c.2797C>T	p.Arg933*	26	Substitution
c.3213dupC	p.Gly1072Argfs*9	33	Duplication, Frameshift
c.3283C>T	p.Arg1095*	35	Substitution
c.3356_7insT	p.Gly1122Argfs*145		Insertion, Frameshift
c.3363_3364insC	p.Gly1122Argfs*32	35	Insertion, Frameshift
c.3364_3371delGGCCC(	p.Gly1125Argfs*142	35	Deletion, Frameshift
c.3459dupC	p.Gly1154Argfs*110		Duplication, Frameshift
c.3509-3518delCAGGG(	p.Pro1170Glnfs*38	36	Deletion, Frameshift
c.3544+3A >C		36	Substitution
c.3690G>A and c.4063_	p.W1230* and p.L1355\	???, 41	Deletion, Frameshift
c.3811C>T	p.Gln1273*	40	Substitution
delEx41		41	Deletion
c.4063_4064delCT	p.Leu1355Valfs*72	41	Deletion, Frameshift
c.4173G>A			Substitution
c.4374_4387del	p.Ser1459Alafs*9	43	Deletion, Frameshift
c.4494_4497insTGCC	p.Ala1499Cysfs*14	43	Insertion, Frameshift
c.4759_4760delTC	p.L1587Vfs*72	40	Deletion, Frameshift
c.4181G>A			Substitution
c.2960_2969dup, c.351	p.Gly991Argfs*96, p.Leu1172Valfs*72, Pro537Glnfs*16 and p. Glu1498Lys*fs		Duplication, Deletion, Frameshift
c.5512C>G, c.5882G>A	His1838Asp, p.Gly1961Glu		Substitution
c.2230C>T	p.Arg744Ter		Substitution
c.2673C>A	p.Cys891Ter		Substitution
c.3307G>A	p.(Gly1103Arg)		Substitution
c.985G>T	p.(Gly329Cys)		Substitution
c.940_942delATC	p.(Ile314del)		Deletion
c.1003C>T	p.(Arg335Ter)		Substitution
c.14315C>G	p.(Ser4772Ter)		Substitution
c.79delA	p.(Thr27Profs*26)		Deletion, Frameshift
c.1107delA	p.(Glu370Asnfs*5)		Deletion, Frameshift

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c.1–23706_373–709delinsTGG			Deletion, insertion		
c.284G > A	p.(Arg95His)		substitution		
c.679C > T	p.(Arg227Trp)		substitution		
c.2459A > G	p.(Gln820Arg)		substitution		
c.1774G > A	p.(Gly592Ser)		substitution		
c.3514_3515delCT	p.(Leu1172Valfs*72)		Deletion, frameshift		
c.678delT	p.(Asn226Lysfs*38)		Deletion, frameshift		
c.1861C > T	p.(Gln621Ter)		Substitution		
PAK2 c.1303 G>A	p.(Glu435Lys)		Substitution		
c. 2_4del	p.?		Deletion		
c.718G>A	(p.Gly240Arg)		Substitution		
c.2134C>T	p.Arg712*		Substitution		
c.2673del	p.Gly892Aspfs*17		Deletion, Frameshift		
c.4290_4299del	p.(Gly1431Glufs*9)	35/41	Deletion, Frameshift		
c.4259-28_4265del		34/41	Deletion		
c.4759_4760del	p.(Leu1587Valfs*72)	39/41	Deletion, Frameshift		
c.4579C > T	p.(Gln1527*)	32/63	Substitution		
c.1487dup	p.(Asn496Lysfs*15)	63/11	Duplication, Frameshift		
c.6151C > T	p.(Arg2051*)	43/63	Substitution		
c.1494_1504del	p.(Gly499Valfs*8)	63/11	Deletion, Frameshift		
c.4171_4172del	p.(Arg1391Glyfs*19)	29/63	Deletion, Frameshift		

Methodology

A review of the literature was conducted from 1992 to 2021 and all the papers accomplishing the inclusion criteria and published by the International scholars were considered. The search strategy adopted was an article title/keyword/abstract-based search using the following key terms: 'Knobloch/recessive and dominant', 'Knobloch/congenital', 'Knobloch /congenital ophthalmological disorders'. KNO1 reported under the study title of birth defects, ophthalmological disorder, and congenital ocular deformities were included. PubMed, Science Direct, and Google Scholar were the search engines employed for literature search. The appropriate information including authors, institute, study site, time, sample size, age group, objectives, and management strategy, was extracted. Data were maintained in excel sheet.

Clinical Techniques

Radiological examinations, CT scan, Optical Coherence Tomography (OCT), Anomaloscope plate test-5, histological examinations, ophthalmic evaluation, magnetic resonance imaging MRI, chest radiography, Echocardiogram, intelligence tests, abdominal ultrasounds, renal and cranial ultrasounds, ELISA to measure plasma concentrations, urinary tract ultrasound scan, vertebral column radiography, slit-lamp biomicroscopy, fundus photography, B scan ultrasonography, Goldmann kinetic perimetry dark adaptometry, Ganzfeld ERGs, LKC technologies, skull radiography, ocular examinations, fluorescein angiography, ultra-sonographic investigations during pregnancy, pathological analysis, psychometric evaluations, retinopathy, teeth examinations, fundus finding after pars plana vitrectomy, DNA extraction, electroencephalography, retinoscopy, vitreoretinopathy, goniotomy, trabeculotomy, auditory screening, gonioscopy were used to determine the clinical symptoms in Knobloch patients.

Genetic Molecular Techniques

RNA purification by Guanidium isothiocyanate method, PCR , silver staining for PCR production visualization, genotype analysis using polymorphic markers, dbEST database searching, bidirectional sequencing through PCR, SSCP analysis of chromosomes, DNA sequencing through Dye Deoxy Terminator Cycle Sequencing, RFLP analysis, Pyrosequencing, flanking primers through primer 3 for mutational analysis, standard chromosome testing, fish analysis, CD68 staining, direct sequencing of COL18.A1 exons, surface plasma resonance assays, immunohistochemistry, RT PCR analysis, BLAST (NCBI) for sequence retrieval, PFAM, GenBank, knockout analysis to determine if knocking out of the gene COL18.A1 has any outcome on expression, autozygosity mapping along with exome sequencing, SNP genotyping, RNA in situ hybridization, Illumina sequencing, whole-genome genotyping, confirmatory sanger sequencing, genotyping and linkage analysis,

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mitochondrial DNA sequencing, segregation analysis, western blotting procedures were used for the mutational analysis of patients' genome.

Mouse Modelling

In recent years, mouse modeling has been performed for the functional analysis of COL18.A1 which is a causative gene for Knobloch syndrome, confirmed through genomic molecular analysis of several Knobloch patients. Col18.a1 directs the conformation of the protein to make a protein named collagen. Absence of collagen and its derivative endostatin results in the underdevelopment of retina and retinal vessels as well as blood vessels in the ophthalmic vitreous region. Dissociation of hyaloid vessels from the surface of the retina, leading to retinal vasculature (13)(15), and absence of VHP capillaries was evident in col18.a1 null mice which were homozygous mutant. Similarly, collagen 18 null mice also showed signs of structural anomalies along inner eye membranes and delayed expression of vascular endothelial growth factors in the retina (12). Ocular examination of Col18.a1 null mice at the age of 22 months showed varied phenotypes and irregularities when compared with wild-type species. Abnormalities included a detachment of layers of IPE cells from the iris, abnormal developmental pattern, and irregular bending of retinal vessels. Mutant mice also showed an unusual increase in thickness of BM zone present in the anterior region of iris (13)(14)(15). Ophthalmic studies along with fluorescence angiography in Col18.a1null mice also showed pigmented regions formed by the migration of cells from iris stroma leading to cluster formation and giving the appearance of iris clumps, thus blocking light from retinal vessels (13)(15). Utrianen et al in 2004 experimentally showed that Col18.a1 null mice also exhibit abnormal skull enlargements as well as irregularities associated with renal structure and functions (14). The latest evidence also shows the signs of iris atrophy and ciliary body abnormalities in collagen 18 null mice which are evident symptoms in Knobloch patients (15). Col18a1 mice and Hspg2 mutant mice were taken under observation out of which col18a1 mice have raised plasma triglycerides comparatively to that of wild type. Hypertriglyceridemia is encountered in mice due to deficiency of col18. Hypertriglyceridemia was developed due to amended extrahepatic clearance triglyceride-rich lipoproteins. In col18a1 mice, the level of lipoprotein lipase (lpl) is notably low in comparison to wild-type mice. Since the Col18a1 mice had hypertriglyceridemia, and a decrease in plasma and endothelium-bound Lpl levels in their blood; this evoked to be tested on human patients who had Col18-deficiency (16). Several anomalies were observed in collagen 18 null mouse eyes. The excessive protrusion was visible from the anterior side of the lens capsule. An examination through a Transmission electron microscope indicated an uncontrolled fibrillar stuff accumulation in an aqueous medium besides the ciliary body of transgenic mice also some inflammation was seen in the fibrillar space on top of the lens capsule. Some retinal and vitreous anomalies were suspected and encountered too. Shortage of collagen 18 resultantly gives led to enlarged eyes, lens subluxation, and lower intraocular pressure. Knobloch sufferers generate truncated protein as a result of missense mutations; they might be deleterious and harmful, this is all disclosed due to the transgenic mice's study in which overexpression of the Tsp-1 domain or the C-terminal endostatin domain was seen (17).

Treatment

Moreover, some common abnormalities in patients with Knobloch syndrome-like cataracts, encephaloceles, blurred vision, etc. can be treated accordingly. Cataract surgery was performed on a Caucasian boy aged 12 years reported with Knobloch syndrome which improved its visual acuity in the right eye to 20/200 (18). Similarly high myopic conditions can be treated with eye surgeries to enhance vision but require proper evaluation from patient to patient (19). Likewise, Ebrahimiadib et al reported a case of an Afghani girl aged 7 years who was suffering from Knobloch syndrome confirmed through genetic testing having severe retinal detachment, underwent medical treatment including scleral buckling surgery and cryotherapy in her left eye. She showed signs of effective retinal detachment repair and improved visual impairment a few months post-surgery (20). Alsulaiman et al in 2019 published a paper that discusses the surgical treatments given to patients having retinal detachment within the timeframe of 7 years (January 2012 till December 2018).

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Different treatment procedures included silicone oil tamponade with scleral buckling surgery or devoid of it, pars plana vitrectomy (PPV), endolaser photocoagulation, retinectomy, triamcinolone-assisted posterior hyaloid peeling, and vitrectomy. 7 out of 9 eyes underwent operative treatments, which couldn't be performed on the rest of two because one had a retinal detachment that was restricted to the atrophic lesion and in the other case, the parent's consent was not available. Post-surgical procedures, 5 out of 9 eyes showed re-attachment of the retina, and two eyes showed re-detachment (21).

Discussion

The relationship of occipital encephaloceles and vitreoretinal degeneration with high nearsightedness and retinal separation was portrayed first by Knobloch and Layer in 1971. As they reported 5 siblings out of 10 in a family showed the above-mentioned conditions i.e. occipital encephaloceles and vitreoretinal degeneration with high myopia. The vitreoretinal degeneration with high nearsightedness and inevitable retinal separation or say detachment are all universally inclusive in this syndrome. The study inferred that innate occipital scalp defects in preference to genuine encephaloceles may, as is valid at times of Meckel condition, go with Knobloch syndrome (22). Clinical flexibility is available in the appearance of this syndrome's condition (23). COL18A1 is situated on the long arm of chromosome 21 (chr21q22.3) and is made out of 43 exons. It encodes the collagen XVIII protein, which has been disclosed to be a significant part of base films (24). COL18A1 has no less than three particular isoforms of various lengths. Regardless of the fact that COL18A1 is pervasively communicated or expressed, its isoforms have distinctive tissue and formative circulation. In expansion to these three isoforms, COL18A1 can create endostatin through proteolytic cleavage. Endostatin is a gesturing molecule known to hinder the relocation and expansion of endothelial cells and is fit for stifling angiogenesis (25)(26). Through genetic investigations it has been noticed that most common mutations occur at exons 30 through 42 of COL18A1; in Knobloch condition patients. In any case, there stays a lot of heterogeneity in mutational site conveyance (27). With advancements in research recently it has also been observed that germline compound heterozygous mutations were likewise portrayed in patients with Knobloch condition (28). Some accessory anomalies in certain patients have been noticed by Caglayan A. O et al 2014; anomalies included atrial septal imperfections, seizures, and minor dysmorphic discoveries/findings. These findings foreground the huge phenotypic range that the Knobloch condition can include and can further represent the significance of type XVIII collagen in the typical improvement of various organ frameworks (29). In this study, we have thoroughly considered case reports of Knobloch syndrome patients till now. We deliberated the reports being mentioned in research papers from 1982 to 2021 and from those cases the symptoms were extracted out as shown in the table. This is collective data that is representing the most common and least commonly occurring symptoms in people being affected by Knobloch syndrome. Not only symptoms, but our analysis also highlights the major causes of Knobloch syndrome and techniques that have been used to track out this syndrome. By performing throughout analysis of all cases; the basic understanding of this syndrome is described in our study. Knobloch syndrome is a condition that is comprised of various ocular defects as well as several clinical abnormalities.

Results

A total of 83 articles have been published on Knobloch syndrome since 1971 out of which we reviewed the cases reported in patients to date. To the best of our knowledge, 49 case reports have been published in literature which reports a total of approximately 240 patients of this ophthalmic disorder up till now. Molecular techniques that were involved in determining the clinical findings in the patients of Knobloch syndrome included clinical molecular techniques and genetic molecular techniques.

Future Recommendations

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As it is evident that Knobloch syndrome involves ocular abnormalities that vary among patients but high myopia, encephaloceles, and occipital defects are the most common symptoms of this condition (30). Because a lot of mutations are a cause of this particular disorder, there is no specific treatment introduced to tackle these kinds of mutations, however, genome sequencing can tell us about the faulty gene and precautions can be taken in this regard. The incidence of inherited genetic disorders among children from a consanguineous marriage is double the rate of children from parents that are not related to each other (31). Consanguinity can be eluded to avoid such genetic disorders.

References

1. Wilson, C., Aftimos, S., Pereira, A., & McKay, R. (1998). Report of two sibs with Knobloch syndrome (encephalocoele and viteroretinal degeneration) and other anomalies. American journal of medical genetics, 78(3), 286–290. https://doi.org/10.1002/(sici)1096-8628(19980707)78:3<286::aid-ajmg16>3.0.co;2-b
2. Aldahmesh, M. A., Khan, A. O., Mohamed, J. Y., Levin, A. V., Wuthisiri, W., Lynch, S., McCreery, K., & Alkuraya, F. S. (2013). No evidence for locus heterogeneity in Knobloch syndrome. Journal of medical genetics, 50(8), 565–566. https://doi.org/10.1136/jmedgenet-2013-101755
3. Seppinen, L., & Pihlajaniemi, T. (2011). The multiple functions of collagen XVIII in development and disease. Matrix Biology, 30(2), 83-92.
4. Keren B, Suzuki OT, Gerard-Blanluet M, et al. CNS malformations in Knobloch syndrome with splice mutation in COL18A1 gene. Am J Med Genet. 2007; 143A:1514-1518.
5. Schuch, G., Heymach, J. V., Nomi, M., Machluf, M., Force, J., Atala, A., ... & Soker, S. (2003). Endostatin inhibits the vascular endothelial growth factor-induced mobilization of endothelial progenitor cells. Cancer research, 63(23), 8345-8350.
6. Sertié, A. L., Quimby, M., Moreira, E. S., Murray, J., Zatz, M., Antonarakis, S. E., & Passos-Bueno, M. R. (1996). A gene which causes severe ocular alterations and occipital encephalocele (Knobloch syndrome) is mapped to 21q22.3. Human molecular genetics, 5(6), 843–847. https://doi.org/10.1093/hmg/5.6.843
7. Ran, M., Weng, B., Cao, R., Li, Z., Peng, F., Luo, H., ... & Chen, B. (2018). miR-26a inhibits proliferation and promotes apoptosis in porcine immature Sertoli cells by targeting the PAK2 gene. Reproduction in Domestic Animals, 53(6), 1375-1385.
8. Antonarakis, S. E., Holoubek, A., Rapti, M., Rademaker, J., Meylan, J., Iwaszkiewicz, J., Zoete, V., Wilson, C., Taylor, J., Ansar, M., Borel, C., Menzel, O., Kuželová, K., & Santoni, F. A. (2021). Dominant monoallelic variant in the PAK2 gene causes Knobloch syndrome type 2. Human molecular genetics, ddab026. Advance online publication. https://doi.org/10.1093/hmg/ddab026
9. Wang, Y., Zeng, C., Li, J., Zhou, Z., Ju, X., Xia, S., ... & Sun, Z. S. (2018). PAK2 haploinsufficeincy results in synaptic cytoskeleton impairment and autism-related behavior. Cell reports, 24(8), 2029-2041.
10. Pollazzon, M., Grosso, S., Papa, F. T., Katzaki, E., Marozza, A., Mencarelli, M. A., ... & Renieri, A. (2009). A 9.3 Mb microdeletion of 3q27. 3q29 associated with psychomotor and growth delay, tricuspid valve dysplasia and bifid thumb. European journal of medical genetics, 52(2-3), 131-133.
11. Zhang, K., Wang, Y., Fan, T., Zeng, C., & Sun, Z. S. (2020). The p21-activated kinases in neural cytoskeletal remodeling and related neurological disorders. Protein & Cell, 1-20.
12. Fukai, N., Eklund, L., Marneros, A. G., Oh, S. P., Keene, D. R., Tamarkin, L., Niemelä, M., Ilves, M., Li, E., Pihlajaniemi, T., & Olsen, B. R. (2002). Lack of collagen XVIII/endostatin results in eye abnormalities. The EMBO journal, 21(7), 1535–1544. https://doi.org/10.1093/emboj/21.7.1535
13. Marneros, A. G., & Olsen, B. R. (2003). Age-dependent iris abnormalities in collagen XVIII/endostatin deficient mice with similarities to human pigment dispersion syndrome. Investigative ophthalmology & visual science, 44(6), 2367–2372. https://doi.org/10.1167/iovs.02-1180
14. Utriainen, A., Sormunen, R., Kettunen, M., Carvalhaes, L. S., Sajanti, E., Eklund, L., Kauppinen, R., Kitten, G. T., & Pihlajaniemi, T. (2004). Structurally altered basement membranes and hydrocephalus in a type XVIII collagen deficient mouse line. Human molecular genetics, 13(18), 2089–2099. https://doi.org/10.1093/hmg/ddh213
15. Marneros, A. G., & Olsen, B. R. (2005). Physiological role of collagen XVIII and endostatin. FASEB journal : official publication of the Federation of American Societies for Experimental Biology, 19(7), 716–728. https://doi.org/10.1096/fj.04-2134rev
16. Bishop, J. R., Passos-Bueno, M. R., Fong, L., Stanford, K. I., Gonzales, J. C., Yeh, E., Young, S. G., Bensadoun, A., Witztum, J. L., Esko, J. D., & Moulton, K. S. (2010). Deletion of the basement membrane heparan sulfate proteoglycan type XVIII collagen causes hypertriglyceridemia in mice and humans. PloS one, 5(11), e13919. https://doi.org/10.1371/journal.pone.0013919
17. Aikio, M., Hurskainen, M., Brideau, G., Hägg, P., Sormunen, R., Heljasvaara, R., Gould, D. B., & Pihlajaniemi, T. (2013). Collagen XVIII short isoform is critical for retinal vascularization, and

overexpression of the Tsp-1 domain affects eye growth and cataract formation. Investigative ophthalmology & visual science, 54(12), 7450–7462. https://doi.org/10.1167/iovs.13-13039

18. Bongiovanni, C. S., Ferreira, C. C. S., Rodrigues, A. P. S., Fortes Filho, J. B., & Tartarella, M. B. (2011). Cataract surgery in Knobloch syndrome: a case report. Clinical Ophthalmology (Auckland, NZ), 5, 735.
19. https://stanfordhealthcare.org/medical-conditions/eyes-and-vision/high-myopia/treatments.html
20. Ebrahimiadib, N., Modjtahedi, B. S., Ferenchak, K., Papakostas, T. D., Mantagos, J. S., & Vavvas, D. G. (2017). Optical coherence tomography findings and successful repair of retinal detachment in Knobloch syndrome. Digital journal of ophthalmology: DJO, 23(1), 29–32. https://doi.org/10.5693/djo.02.2017.01.002
21. Alsulaiman, S. M., Al-Abdullah, A. A., Alakeely, A., Aldhibi, H., Engelbrecht, L., Ghazi, N. G., & Mura, M. (2020). Macular Hole-Related Retinal Detachment in Children with Knobloch Syndrome. Ophthalmology. Retina, 4(5), 498–503. https://doi.org/10.1016/j.oret.2019.12.004
22. Seaver, L. H., Joffe, L., Spark, R. P., Smith, B. L., & Hoyme, H. E. (1993). Congenital scalp defects and vitreoretinal degeneration: redefining the Knobloch syndrome. American journal of medical genetics, 46(2), 203-208.
23. Sniderman, L. C., Koenekoop, R. K., O'Gorman, A. M., Usher, R. H., Sufrategui, M. R., Moroz, B., ... & Der Kaloustian, V. M. (2000). Knobloch syndrome involving midline scalp defect of the frontal region. American journal of medical genetics, 90(2), 146-149.
24. Halfter, W., Dong, S., Schurer, B., & Cole, G. J. (1998). Collagen XVIII is a basement membrane heparan sulfate proteoglycan. Journal of Biological Chemistry, 273(39), 25404-25412.
25. Suzuki, O. T., Sertie, A. L., Der Kaloustian, V. M., Kok, F., Carpenter, M., Murray, J., ... & Passos-Bueno, M. R. (2002). Molecular analysis of collagen XVIII reveals novel mutations, presence of a third isoform, and possible genetic heterogeneity in Knobloch syndrome. The American Journal of Human Genetics, 71(6), 1320-1329.
26. Schuch, G., Heymach, J. V., Nomi, M., Machluf, M., Force, J., Atala, A., ... & Soker, S. (2003). Endostatin inhibits the vascular endothelial growth factor-induced mobilization of endothelial progenitor cells. Cancer research, 63(23), 8345-8350.
27. Suzuki, O., Kague, E., Bagatini, K., Tu, H., Heljasvaara, R., Carvalhaes, L., ... & Passos-Bueno, M. R. (2009). Novel pathogenic mutations and skin biopsy analysis in Knobloch syndrome. Molecular vision, 15, 801.
28. Joyce, S., Tee, L., Abid, A., Khaliq, S., Mehdi, S. Q., & Maher, E. R. (2010). Locus heterogeneity and Knobloch syndrome. American journal of medical genetics. Part A, 152(11), 2880-2881.
29. Caglayan, A. O., Baranoski, J. F., Aktar, F., Han, W., Tuysuz, B., Guzel, A., ... & Gunel, M. (2014). Brain malformations associated with Knobloch syndrome—review of literature, expanding clinical spectrum, and identification of novel mutations. Pediatric neurology, 51(6), 806-813.
30. White, R. J., Wang, Y., Tang, P., & Montezuma, S. R. (2017). Knobloch syndrome associated with Polymicrogyria and early onset of retinal detachment: two case reports. BMC ophthalmology, 17(1), 214. https://doi.org/10.1186/s12886-017-0615-z
31. Merten, M. (2019). Keeping it in the family: consanguineous marriage and genetic disorders, from Islamabad to Bradford. BMJ: British Medical Journal (Online), 365.