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# Clinical Spectrum and Genetics of Nanophthalmos: A Review

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## Abstract

Nanophthalmos is a clinical diapason of diseases with a phenotypically small but structurally normal eye. These diseases present significant clinical challenges to ophthalmologists due to a high rate of secondary angle check glaucoma, robotic choroidal effusions, and perioperative complications with cataract and retinal surgeries. Nanophthalmos may present as a sporadic or domestic complaint, with autosomal dominant or sheepish heritage. To date, five genes (i.e., MFRP, TMEM98, PRSS56, BEST1 and CRB1) and two loci have been intertwined in domestic forms of nanophthalmos. Then, we review the description of nanophthalmos, the clinical and pathogenic features of the condition, and the genetics of this complaint.

**Keywords:** Nanophthalmos; Ophthalmologists; Eye; Surgeries

## Introduction

The clinical diapason of the small eye phenotype comprises conditions in which there's a global optical reduction in size (e.g., microphthalmos and nanophthalmos) or shortening of either the anterior or posterior parts of the eye (e.g., relative anterior and posterior microphthalmos, resp.). The axial length and anterior chamber structures present a continuum of sizes, where microphthalmos and nanophthalmos comprise the lowest or shortest eyes. Nanophthalmos derives from Greek “dwarf eye”. In this optical condition, the anterior and posterior parts have no other natural deformations, but are both reduced in size, with secondary thickening of choroid and sclera [1].

Another individual issue that has been batted in the literature is the distinction between nanophthalmos and posterior microphthalmos. Posterior microphthalmos is described as a subtype of microphthalmia, in which the axial length is docked in the posterior member only. In this condition, the anterior member of the eye has normal depth and angle configuration. Some investigators consider that nanophthalmos and posterior microphthalmos are synonymous. The report that the reduction of the corneal periphery in high presbyopia is commensurable to the axial shortening of the eye supports the thesis that these realities represent instantiations of the diapason of presbyopia, rather than two fully different conditions. In addition, the fact that mutations in the same genes may beget both posterior microphthalmos and nanophthalmos reinforces this idea still, other groups point to the clinical and structural differences between these conditions, similar as the cornea size and curve, anterior chamber depth, lens consistence, angle characteristics, and propensity for complications. Relhan biometrically anatomized eyes of 38 cases with high presbyopia (defined in the study as lesser than7.00 D globular fellow on refraction), all of them with an axial length equal or lower than 20.5 mm. In this study, they defined the cases with corneal compasses below 11.0 mm as nanophthalmic and those with corneal compasses lesser than or equal to11.0 mm as posterior microphthalmos. They set up that nanophthalmic eyes have shallow anterior chamber depth, thicker lens, and steeper cornea, in comparison with posterior microphthalmic eyes. They also reported different tendencies to complications the prevalence of angle- check glaucoma was 69.23 in the nanophthalmos group versus 0 in the posterior microphthalmos group, while the prevalence of macular crowds was 0 versus 24, independently [2].

In addition to these clinical features, nanophthalmic eyes have abnormal collagen fibrils in each of the three layers of the sclera. These abnormal filaments are allowed to be the cause for the increase scleral consistence as mentioned over. In addition, the combination of increased scleral consistence and abnormal collagen also contributes to its inelasticity, which impairs whirlpool venous drainage and reduces transcleral inflow of proteins. These histopathologic features and deconstruction described over are allowed to be the medium by which nanophthalmic eyes develop complications of angle- check glaucoma, uveal effusion pattern, and retinal detachment. still, it's unclear whether the abnormal scleral structure is a primary or secondary effect of the inheritable changes that induce nanophthalmos as numerous of the genes intertwined in this condition are expressed in retina and retinal color epithelium [3].

Other optical findings include topographic corneal steepening and irregular presbyopia, absent or rudimentary foveal avascular zone, optical slice drusen, retinoschisis and foveoschisis and Retinitis Pigmentosa (RP), crowded optical fragment, chorioretinal crowds, and retinal excrescencies, central retinal tone occlusion, increased subfoveal choroidal consistence, and abnormalities in the retinal layers ’ consistence and distribution.

In summary, the described anatomical features and histopathology of the nanophthalmic eye explain the severe visual consequences in individualities with nanophthalmos. However, also this results in unrecoverable amblyopia, If the axial presbyopia isn't corrected in early nonage. The uncelebrated and undressed angle check glaucoma can lead to progressive optical whim-whams damage and blindness. Likewise, intraocular surgeries in nanophthalmic eyes have significant pitfalls and complications, both intraoperatively and postoperatively. Proper preoperative planning and anatomic understanding can lead to good issues and bettered quality of life in these cases, despite a nearly 40-60 rate of intraoperative complications [4].

## Inheritable aspects of Nanophthalmos

Nanophthalmos occurs due to arrested development of the eye

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in the early stages of embryogenesis. It's allowed to have a strong inheritable base. There are numerous reported domestic cases with autosomal- dominant and sheepish forms of heritage. Still, nanophthalmos can also do as a sporadic condition, which may represent either environmental goods or physical or new mutations that affect in arrest of optical growth.

To date, five inheritable loci were reported to be linked to nanophthalmos NNOS 2 is related to mutations in Membrane Frizzled Affiliated Protein (MFRP); NNOS 4 is related to mutations in TMEM98; MCOP6 is related to mutations in serine protease 56 (PRSS56); and NNOS 1 and 3 were localized to chromosomal regions only (11p12- 11q13 and 2q11- q14). Two fresh genes, CRB1 and BEST1 (VMD2), have been intertwined in nanophthalmos and have profound places in photoreceptor and Retinal Color Epithelial (RPE) function, independently [5].

## Membrane Type Frizzled-Affiliated Protein Gene (MFRP)

A significant number of cases of sheepish nanophthalmos have been assigned to mutations in the Membrane Type Frizzled Affiliated Protein gene (MFRP, OMIM 606227). This gene is located in chromosome 11q23 and encodes a glycosylated trans membrane protein that has an extracellular frizzled-affiliated cysteine-rich sphere. Frizzled proteins are receptors involved in the regulation of growth, isolation, and cell opposition during development through the signalling pathway.

In humans, the MFRP gene is expressed in the retinal color epithelium and in the ciliary body. Outside of the eye, it can only be set up at veritably low situations in the brain, likely account for the localized optical phenotype in MFRP insufficiency. This gene seems to play an important part in both the optical growth during nonage, performing as a controller of optical size. It also has a part in conservation of the RPE, which supports photoreceptor function. Mouse models of MFRP insufficiency, similar as rd6 (Mfrprd6) and rdx (Mfrp174delG) mice, have blotched retina diseases and photoreceptor degeneration, supporting the significance of this gene for retinal and RPE physiology [6].

The link between eye size and RPE/ciliary body function has yet to be illustrated. It has been proposed that MFRP affects the physiologic medium of emmetropization, in which the refractive error is corrected by postnatal axial growth during the first six times of life. Soundrarajan suggested that a complex nonsupervisory network may impact the postnatal eye development and indicated the participation of another gene (PRSS56) in the same pathway. Besides these, other proposed mechanisms for the part of the RPE/ciliary body in eye size include the mechanical stress goods and the seditious response observed in the retina. Most lately, Velez set up that introducing a normal dupe of MFRP gene through adenoviral- grounded gene remedy may reverse some of these pathogenic changes in Mfrp rd6/rd6 mice. Specifically, subretinal injection of this vector redounded in deliverance of photoreceptor death, normalization of retinal function, and regulation of eye length in adult mice. These findings suggest that gene remedy may be a feasible option for this complaint.

Mouse models of Mfrp loss of function have failed to demonstrate the full nano ophthalmic phenotype observed in humans and rather present with predominant retinal degeneration. This may be in part due to the differences in the lens size and optical deconstruction in mice and humans. Collery proposed a new model using zebra fish (Danio rerio) that better mimics the mortal phenotype and may be useful in studying and better understanding this condition [7].

To date, several cases of MFRP mutations leading to reduced eye axial length have been reported. According to Wasmann by the time of the publication in 2014, there were 14 different described MFRP mutations two of them were single amino acid negotiations at extremely conserved spots and 12 caused severe truncation of the protein. Since that time, three new mutations have been described, and fresh given mutations have been reported in other populations. All of these cases presented with high presbyopia, but the effect of the mutation on retinal rod photoreceptor function was different between individualities and the clinical diapason of age of onset and inflexibility of complaint was relatively variable. The reason for this clinical variability may be a combination of the diapason of inheritable mutations in MFRP and other inheritable or environmental modifiers that remain to be determined.

Wasmann reported a case of two sisters with verified MFRP mutations. They both presented low visual perceptivity, high presbyopia, macular retinal crowds, with the aged stock also having thickened sclera, and optical whim-whams head drusen. The mutations in the MFRP gene have also been linked to the autosomal- sheepish pattern of posterior microphthalmos, retinitis pigmentosa, foveoschisis, and optical slice drusen. These results represent the broad clinical diapason of MFRP mutations, which occurs probably due to differences in early gene expression and environmental factors that shape the development of the eye.

## Transmembrane Protein 98 Gene (TMEM98)

The transmembrane protein 98 (TMEM98, OMIM 615949) gene encodes a trans membrane protein that's widely expressed in the mortal body, including in the optical apkins, similar as iris, choroid, retinal color epithelium, and sclera. Its specific function still remains unclear, but it's hypothecated to lead to pathologic scleral pathologic thickening and secondary glaucoma development in nanophthalmic eyes or play a part in the development of the RPE.

In a large birth, Awadalla and associates set up a missense mutation in the TMEM98 (A193P) that could be associated with autosomal dominant nanophthalmos. Although its pathogenic relationship with the complaint wasn't clear, this association has been greatly strengthened by Khorram and associates recent report of two new TMEM98 mutations (His196Pro and c.694_721delAGAATGAA GACTGGATCGAAGATGCCTCgtaagg) in autosomal- dominant nanophthalmic cases. Fresh studies are still demanded to identify the specific part of this gene in the pathogenesis of nanophthalmos.

## Protease Serine 56 (PRSS56)

PRSS56, also known as LOC646960, is located in the chromosome 2q37.1 and encodes a protein of 603 amino acids, which functions as a serine protease. It's suggested that it's expressed in the embryonic towel, brain, testis, and eye. There are reports of its association with nanophthalmos and posterior microphthalmos cases although its physiologic and pathogenic mechanisms remain to be completely determined [8].

It has been reported that PRSS56 is largely expressed in retinal ganglion cells of adult creatures, and its presence in this towel and in the brain cells suggest its applicability in the regulation of optical development. Nair demonstrated this part in the homozygous mutant mice Prss56Grm4, which showed docked axial length and advanced vulnerability to angle check. Likewise, they set up that the differences in optical size between mutant mice and wild- type controls were precipitously lesser after birth, with no significant difference previous to that time. They set up that the inheritable background had a strong influence of magnitude of eye size differences between wild- type

and mutant mice, suggesting the actuality of inheritable modifiers that impact eye growth in musicale with Prss56. Soundararajan also suggested that PRSS56 and MFRP may serve through a common natural pathway that affects the emmetropization process, but nature of this commerce is still unclear.

### Crumbs Homologue 1 Gene (CRB1)

mortal CRB1 is a 1406 amino acids transmembrane protein that localizes to photoreceptor inner parts and is vital for the neuronal development of the retina. The CRB1 gene is located in chromosome 1, in the interval1q31.2- 1q32.1, and its mutations are classically associated with colorful inheritable retinal dystrophies, including Leber natural Amaurosis. likewise, some recent reports showed association of mutation in CRB1 with nanophthalmos and retinitis pigmentosa.

### Bestrophin 1 (BEST1/VMD2)

The BEST1 (VMD2) gene is located on chromosome 11q12 and is primarily expressed in the RPE. It encodes an integral membrane protein, bestrophin 1, localized generally in the basolateral tube membrane of the RPE and most prominently near the macula. BEST1 mutations are classically associated with Stylish Vitelliform Macular Dystrophy (BVMD), a complaint confined to the macula. Still, it has been reported to be in association with other wide optical abnormalities, similar as Autosomal Dominant Vitreoretino Choroidopathy (ADVIRC) and Autosomal Sheepish Bestrophinopathy (ARB), which are both associated with nanophthalmos. Other studies also explosively suggest an association between BEST1 mutations and angle check glaucoma [9].

ADVIRC is a rare condition characterized by a supplemental circumferential hyperpigmented band with punctate white darkness in the retina, chorioretinal atrophy in the midperipheral or peripapillary retina, and vitreous fibrillary bowdlerizations. There are reports of association of this condition with nanophthalmos and a advanced prevalence of angle check glaucoma.

ARB is also a rare condition characterized by macular and midperipheral subretinal whitish to unheroic deposits that may come scars and lead to drop in visual perceptivity. Cases are generally hypermetropic and have a shallow anterior chamber and a advanced propensity to angle- check glaucoma.

### Other Loci for Nanophthalmos

The autosomal dominant nanophthalmos N NO1 (OMIM 600165) is caused by a disfigurement on chromosome 11, between D11S905 and D11S987. This region may also be associated with inflexibility of angle check glaucoma instantiations. The precise inheritable change at this locus has yet to be verified, though rendering and nonsupervisory mutations in BEST1 have been barred as a cause. Another form of autosomal dominant complaint, N $NO_3$ (OMIM 611897), was described in a family with simple microphthalmia, micro cornea, and high presbyopia, and it was reported to be linked to chromosome 2q11-14 [10].

## Conclusion

With the progress of the imaging and surgical technologies, there have been significant advances in the opinion and operation of the nanophthalmic eye. These have bettered issues for individualities with similar grueling eyes. likewise, substantial new discoveries in the genetics of nanophthalmos have led to the discovery of numerous new genes and pathways in the pathogenesis of this condition. These advances will eventually ameliorate early discovery of this condition and give new avenues for treatment, including the possibility for gene remedy. inheritable judgments will grease inheritable comforting for domestic forms of this condition and may help to drop amblyopia from uncorrected presbyopia, help vision loss from complications, and ameliorate monitoring to minimize glaucoma and retinal complications from nanophthalmos.

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### Conflict of Interest

The author declares that they have no conflict of interest.

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