

# Cross-sectional observational analysis of the genetic referral practices across pediatric ophthalmology outpatient departments in an urban setting

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**Purpose:** To analyze the genetic referral practices of pediatric ophthalmologists in an urban setting. **Methods:** (1) The first limb of the study: cross-sectional, observational study among children visiting the outpatient department of pediatric ophthalmology across five centers in Mumbai. All pediatric patients were screened separately by pediatric ophthalmologists and a clinical geneticist for their ophthalmic and systemic complaints. Children were marked for referral to genetics (RTG) by both the specialists based on identification of distinctive features (red flag) and were requested to meet a local geneticist. (2a) Twenty-three months later, patients who had been marked for RTG were contacted telephonically to follow-up if they had met the geneticist. (2b) Additionally, the last 20 proformas from each center were checked retrospectively to note the RTG marked by the ophthalmologist alone. **Results:** (1) In the first aspect of the study, 126 patients (male: female = 1.2:1) were included. Forty-nine (38.3%) patients were referred for genetic evaluation, of which three (6.1%), 31 (63.26%), and 15 (30.6%) cases were referred by the ophthalmologist alone, geneticist alone, and by both the specialists, respectively. Glaucoma (100%), nystagmus (86%), and leukocoria (83%) were the most prominent ocular diagnoses in cases referred for genetic evaluation. Facial dysmorphism (55.1%) and neurodevelopmental delays (51%) were among the most common systemic red flags found in patients referred to genetics. (2a) Twenty-three months later, on contacting the 49 patients marked for RTG, only one family had met the geneticist. (2b) Retrospective evaluation of 100 proformas: only three patients were marked for RTG by ophthalmologist alone. **Conclusion:** This study found that the genetic referrals by pediatric ophthalmologist were far lesser than those by geneticist. The study highlights an area of knowledge gap among pediatric ophthalmologists, prompting a need for heightened awareness in this area.

**Key words:** Delayed Diagnosis, genetic counseling, genetic testing, hereditary eye diseases

The last two decades have witnessed significant milestones in the understanding of ocular diseases and their linkages with genetics.<sup>[1]</sup> These developments have considerably impacted the understanding of the genetic basis of structural and functional defects and diseases affecting the eyes. While internationally, the quantum of progress has been very high, ocular genetics is still a relatively nascent field in India.<sup>[1]</sup> The field of pediatric ophthalmology is akin to Pandora's box, as it is filled with thousands of inheritable disorders.<sup>[2]</sup> A pediatric ophthalmologist is frequently faced with ocular conditions with systemic involvement. It may not be uncommon for the pediatric ophthalmologist to give a detailed attention on the symptomatic and ocular management of the patient, while the genetic component may remain largely unexplored.

Given the positive impact of a timely and precise genetic diagnosis for the patient and his/her family and the medicolegal repercussions of delayed referral, there is a need for heightened sensitization toward genetics and its practical nuances among practicing pediatric ophthalmologists.<sup>[2]</sup> In India, sparing premium institutes, there is lack of awareness

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about the important "red flags" toward genetic referrals among this group of physicians. We intended to understand this knowledge gap better, with the aim to address the concern, through systematic sensitization of the pediatric ophthalmologists in this domain in the future. Thus, we designed a cross-sectional observational study across five pediatric ophthalmology outpatient departments (OPDs) to analyze the referral practices toward genetic services among pediatric ophthalmologists.

## Methods

This was a cross-sectional, observational study designed in accordance with the Declaration of Helsinki. The first limb of the study was conducted between October 2019 and December 2019 in the pediatric ophthalmology OPDs across five centers in Mumbai. Of these five centers, two were private clinics and one was a public hospital, while the other two were charitable trust centers. One day was selected for visit by the geneticist

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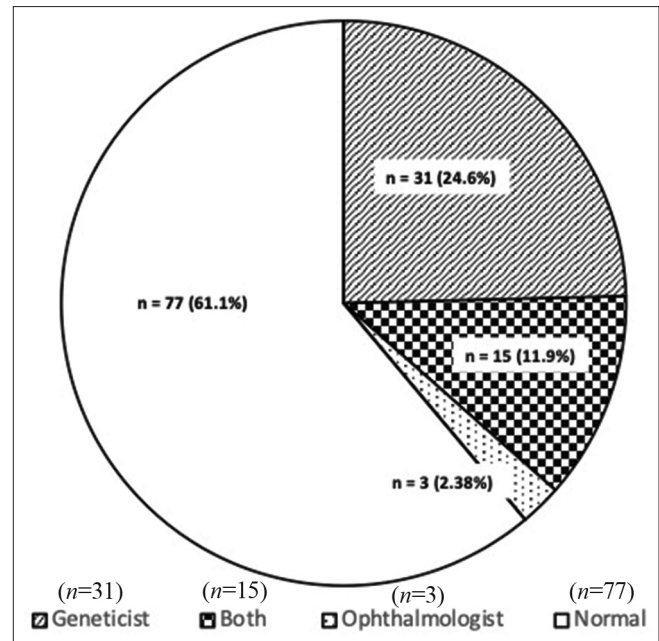
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at each center. All the pediatric patients visiting the OPDs were individually screened at each center on that single day by pediatric ophthalmologists (with an average experience of 20.8 years) and a fellowship-trained clinical geneticist (with 13 years of experience), in that order. Patients' clinical details including their presenting ocular complaints, systemic history, key examination features, and the presence of any distinctive feature (i.e., red flag) that raised a suspicion of a genetic etiology were recorded separately by the pediatric ophthalmologist and the clinical geneticist on a predesigned proforma. Patients' data was collected and the patients who were marked as referral to genetics (RTG) by both the specialists were segregated and analyzed. The ophthalmic features in all the patients who participated in the study were recorded as a separate entity each. For example, in a child presenting with nystagmus, poor vision, and squint, we noted three ocular features. The nonophthalmic red flags in each case among those marked for RTG were recorded separately. For example, in a child with ocular complaints, who had facial dysmorphism and delayed development, these two clues were recorded as separate red flags. At the end of the evaluation, patients marked for RTG by either specialist were counseled to consult a local geneticist. (2a) In the second limb of the study, 23 months later, in November 2021, patients who were marked for RTG were contacted telephonically to follow-up if they had met the geneticist. (2b) Additionally, the last 20 proformas from each center were checked retrospectively to note the number of RTG marked by the ophthalmologist alone.

## Results

We screened a total of 126 patients in this study. The median age of these patients was 5.5 years (range 1 month to 18 years); the male:female ratio was 1.2:1. Clinical history and examination of patients raised an RTG in 49 of the 126 (38.3%) patients. Of these 49 cases, the referral was raised in three (6.1%) cases by the ophthalmologist alone and in 31 (63.26%) cases by the geneticist alone, while the referral was raised by both in 15 (30.6%) cases [Fig. 1]. A total of 146 ophthalmic features were recorded in the 126 patients who participated in the study. The proportion of these ophthalmic features that culminated into an RTG was analyzed [Fig. 2]. Of note, certain ocular features like childhood glaucoma, leukocoria, and nystagmus were marked for RTG almost universally. A total of 108 nonophthalmic red flags categorized into nine main groups were noted for the 49 cases marked for RTG [Fig. 3]. Ophthalmic complaints coexisting along with facial dysmorphisms and neurodevelopmental delays were the most common red flags raising suspicion of an underlying genetic etiology.

Among the 31 referrals raised by the geneticist alone and missed by the ophthalmologist were two children with Down syndrome. They were both not following any formal or comprehensive genetic surveillance. Among some of the cases with predominant/obvious "ophthalmic" handles that were raised for referral only by the geneticist were the following: two cases of congenital cataract; one case of congenital squint associated with short stature, clinodactyly, and hydrocephalus; one case of bilateral optic nerve atrophy associated with cognitive delay and behavioral issues; one child with congenital cone-rod dystrophy and nystagmus; and one case of clinically diagnosed oculocutaneous albinism.



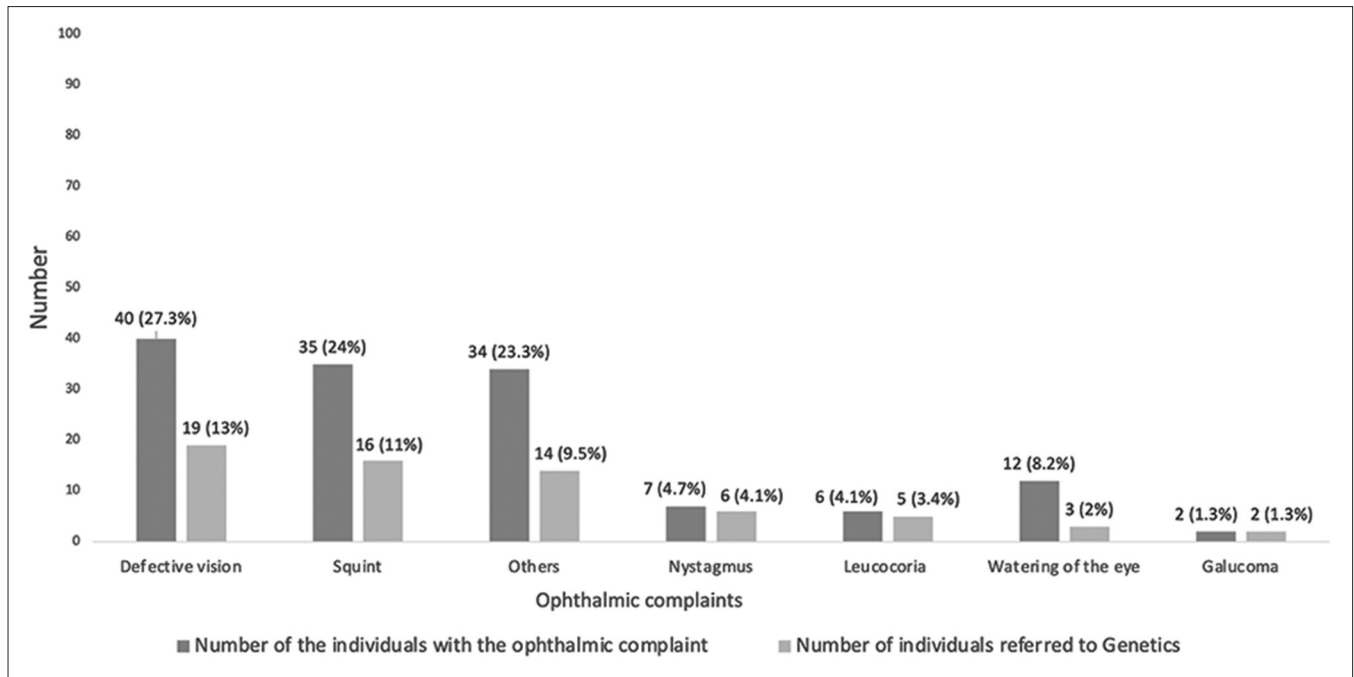
**Figure 1:** Pictorial representation of the number of genetic referrals as assessed in the study. % calculated with n of 126 as the denominator. 31 patients were marked by Geneticists alone, 15 patients were marked by both Geneticists and Ophthalmologists, 3 patients were marked by the Ophthalmologist alone for referral to genetics

(2a) On tracing back the patients marked for RTG, 23 months later, 41 of these could be contacted, of which only one family had met the local geneticist. The family that met the geneticist had their previous child (proband) suffering from retinitis pigmentosa and was concerned about the risk of recurrence of the same in their ongoing pregnancy. The reasons stated by the remaining 40 for not meeting the geneticist included (i) Covid-related restrictions and financial constraints (24 patients), (ii) not being aware of the utility of the test (nine patients), and (iii) accessibility to a geneticist (seven patients).

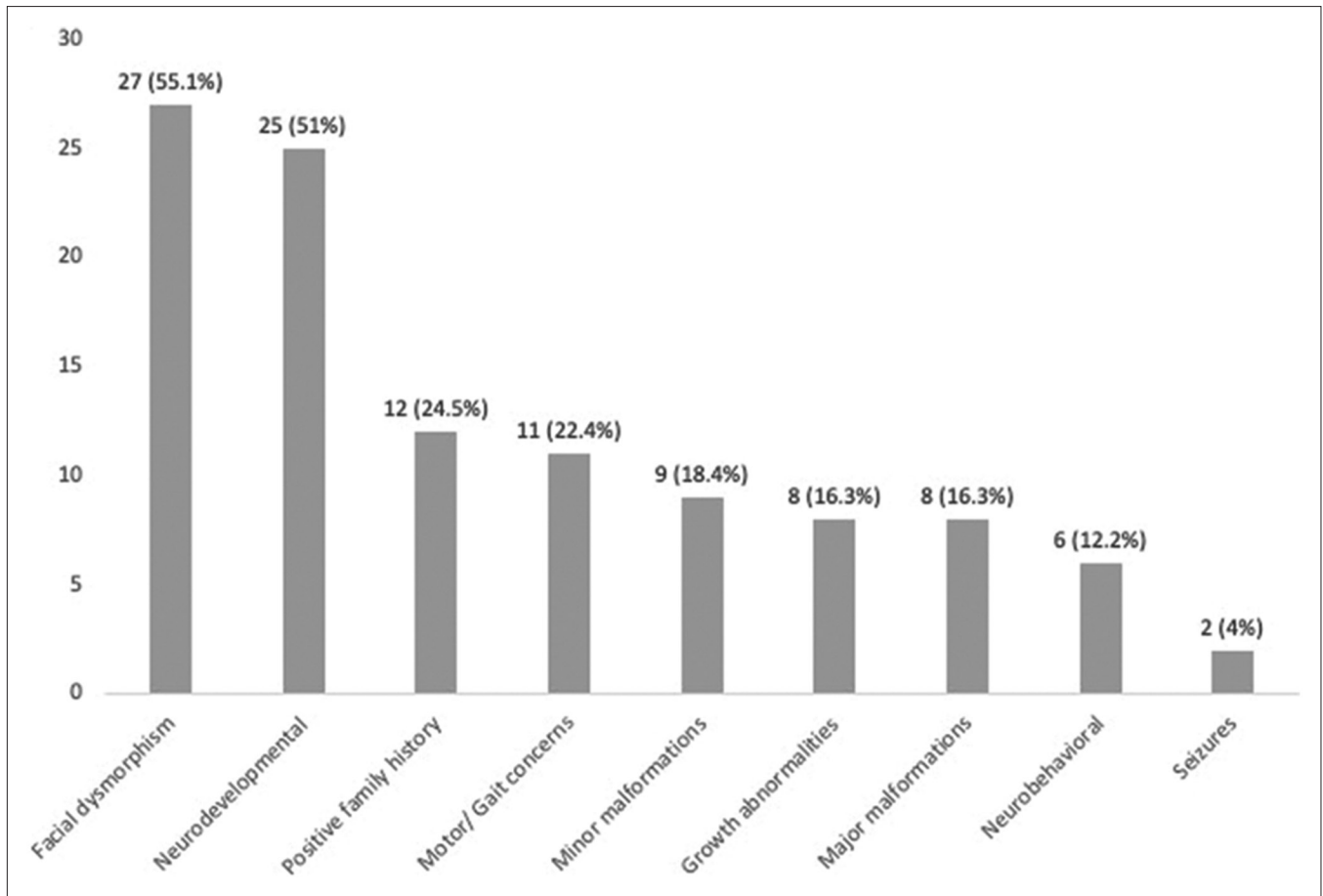
(2b) On retrospective evaluation of latest 100 proformas (20 from each center), only three patients were marked for RTG by ophthalmologist alone. These included a child with Down syndrome, one child with oculocutaneous albinism, and one child with ectrodactyly and squint. In the first limb of the study, the total referrals raised by the ophthalmologist alone included 3/49, while in another 15/49, both the geneticist as well as the ophthalmologist raised the referral. We appreciate 3/100 (3%) figure of RTG by ophthalmologists in 2021, which is far lower than 18/49 (36.73%) total referrals raised by ophthalmologists in 2019.

## Discussion

While considering genetic disorders, the eye is reported to be the second most commonly affected organ, after the brain.<sup>[1]</sup> Prompt and accurate recognition of a suspicious genetic etiology in ocular diseases can guide a rational selection of genetic test from among the vast armamentarium of newer genetic tools: chromosomal microarray (CMA), exome sequencing (ES), and multiplex ligation probe-dependent amplification (MLPA), to name a few.<sup>[2]</sup> Timely genetic diagnosis thus reached can aid accurate genetic counseling about the disease inheritance, risk



**Figure 2:** Bar diagram representing the proportion and percentage of ophthalmic complaints which were referred to the genetic services. X-axis denotes 146 ophthalmic complaints amongst 126 patients. Y- axis denotes number of patients having the particular complaint and the proportion of them referred to genetics. ('Others' represent patients visiting for follow-up or referral for comprehensive eye check-up)



**Figure 3:** Bar diagram representing the number (percentage) of patients referred to genetic services with red flags (features suggesting likelihood of an underlying genetic abnormality). X-axis represents the 49 cases marked for referral to genetics in the study population and Y-axis represents the number of patients with each of the mentioned red flags

of recurrence in the future offspring, mitigation of preventable complications by timely surveillance and intervention, offering therapeutics when available, and lastly, prognostication.<sup>[2]</sup> For example, in a toddler with aniridia, a contiguous deletion of *WT1-PAX6* region confirms the diagnosis of Wilms tumor–aniridia–genitourinary anomalies–mental retardation (WAGR) syndrome in the child.<sup>[3]</sup> Such a diagnosis mandates three-monthly renal ultrasound until 8 years of age for Wilms tumor, a condition that can be potentially lethal if diagnosed late.<sup>[4]</sup> On the other hand, if the aniridia is not attributed to WAGR, but is rather due to an underlying *PAX6*-related “nonsense” mutation, it suggests patient candidacy for an under-research drug, ataluren.<sup>[3]</sup>

Notwithstanding these benefits to the patient, it is also prudent to remember that a delayed referral can effectively amount to failure of duty to refer on part of the treating physician. Not surprisingly, in a recent publication analyzing the medical malpractice cases against otorhinolaryngologists between 2010 and 2019, failure to diagnose, treat, or refer to another appropriate expert was collectively the second most common complaint (32% of 94 cases) raised by the plaintiff.<sup>[5]</sup> By extrapolating these results to ophthalmic practice, the magnitude of patient damages due to delayed diagnosis is not difficult to gauge. For example, inborn errors of metabolism (IEM), many of which can be potentially treatable if diagnosed in time, can often present to the ophthalmologist as premature or congenital cataract, optic atrophy, or retinal changes.<sup>[6]</sup> An unsuspecting approach and the resultant delayed diagnosis in such cases can potentially cause irreversible neurological and/or systemic damage, disability, and sometimes, even early death. Since IEM commonly follow autosomal recessive, and sometimes X-linked recessive inheritance modes, a delayed diagnosis could also cause a recurrence of the same disease in the next pregnancy.<sup>[6]</sup>

Thus, the impact of timely referral and diagnosis to the patient and the physician alike cannot be overemphasized. However, awareness regarding the same, commensurate to impact of the aforementioned factors, is largely missing among pediatric ophthalmologists. A substantiation to this can be reflected from the observations of the present study, wherein even high-yield and relatively easy indicators (Down syndrome, congenital cataract, congenital nystagmus, and evident syndromic handles) were missed from the radar of ‘suspicion’ by the ophthalmologist.

Chasms in understandings of the complexities of genetics among pediatric ophthalmologists can be estimated from a recent survey conducted by the American Association of Pediatric Ophthalmology and Strabismus (AAPOS). In this survey, 90% of the 264 responding pediatric ophthalmologists who ordered a genetic test “themselves” in their practice worked along with a genetic specialist, at least part-time.<sup>[7]</sup> Majority of the respondents who did not order the test themselves referred the patient to a geneticist or an ophthalmologist with genetic expertise. Fourteen percent of the respondents in this AAPOS survey did not order a genetic test at all and continued only with symptomatic and ophthalm-restricted care for the patient.<sup>[7]</sup> Nearly half of the respondents in the AAPOS survey acknowledged not having any understanding of genetic testing modalities and their applications.<sup>[7]</sup>

In the current study, the number of cases marked for RTG by the ophthalmologist alone (6.1%) was nearly one-tenth of those marked by the geneticist (63.26%). The cumulative RTG by the ophthalmologist (36.7%) was less than half of that by the clinical geneticist (93.8%). While we cannot rule out the confounding factor of possible over-referring by both groups, these figures still demonstrate a lower pick-up rate of the red flags toward genetics among pediatric ophthalmologists in the given setting. The possible reasons for lack of referral among pediatric ophthalmologists could be: lack of awareness about the alerts for an underlying genetic condition and about the possible benefits of a timely diagnosis, perceived futility of a genetic referral in the light of genetic conditions not necessarily getting “cured” often, dearth of locally available and accessible genetic specialists, and the financial concern regarding the often out-of-pocket patient expenses toward the genetic tests.

Results of Fig. 2 enable us to appreciate the spectrum of clinical presentations to a pediatric ophthalmologist that can be associated with an underlying genetic etiology. In our study, childhood glaucoma, leukocoria, and nystagmus were nearly universally referred to genetics, appropriately so. It is estimated that about 56%–75% of the congenital cataracts,<sup>[1,8]</sup> 50%–83% of the retinal dystrophies,<sup>[9]</sup> and at least 64% of infantile nystagmus<sup>[10]</sup> have an underlying genetic etiology. Keeping in tune with these high-yield markers, some potential “low-hanging fruits” for genetic association in pediatric ophthalmology, as suggested by AAPOS, are as follows: infantile or developmental cataracts, infantile nystagmus, developmental abnormalities of the eye, coloboma, iris ectropion, primary congenital glaucoma, lens subluxations, optic disk malformations and hypoplasia, high myopia (even if nonsyndromic), and retinal dystrophies.<sup>[4]</sup>

While one may take home from Fig. 2 the high-yield referral indicators toward genetics, the need for heightened suspicion is highlighted by the observation that nearly half of the patients visiting even for seemingly simple (and often unsuspected) follow-up or comprehensive eye check-up were marked for referral in this study (“Others” in Fig. 3). The 14 (out of 49) case profiles marked under this category include the following: (1–3) Down syndrome coming for routine surveillance; (4) neonate with hepatosplenomegaly, microcephaly, facial dysmorphism, direct hyperbilirubinemia; (5) hypoglycemia, infantile spasms, microcephaly, and delayed milestones; (6) post-squint surgery with severe short stature, facial dysmorphisms, and hypotonia; (7) glaucoma with facial dysmorphisms; (8) dystonic cerebral palsy with microcephaly, facial dysmorphism; (9) Crouzon syndrome with meningomyelocele; (10) delayed milestones with facial dysmorphism; (11–12) syndromic congenital heart disease with facial dysmorphism; (13) syndromic attention deficit hyperactivity disorder with facial dysmorphism with cortical visual impairment; and (14) congenital aniridia.

On similar notes, seemingly non-genetic handles like watering of the eye were also flagged for RTG because of the associated underlying systemic features, which were missed until the study. Of the three children in this category, the reasons for a genetic suspicion were as follows: oculocutaneous albinisms (clinically diagnosed) and syndromic craniosynostosis. The third one of these cases was a neonate who had antenatal history of polyhydramnios, intrauterine growth restriction, poor suck and feeding, hypotonia with

depressed deep tendon reflexes, along with nonspecific facial dysmorphisms. Important differentials for this case, as raised by the geneticist, included congenital myopathies and Prader-Willi syndrome.

The second limb of the study conducted 23 months later helped us mark important hurdles in the translation of referrals to actual genetic work-up by the patient families. Improving pretest counseling, clearly outlining the reason for genetic suspicion, the benefits and limitations of the referral and the subsequent tests (if needed), and making genetic services more accessible to all could help diagnose more ocular diseases of genetic origin. The retrospective analysis of 100 proformas, 23 months later, indicated a general poor referral rate among ophthalmologists in the absence of dedicated training modules in this direction.

On studying the red flags among the 49 cases marked for RTG, we appreciate some trainable high-yield parameters. Simple measures like pedigree elicitation, enquiring for systemic abnormalities and malformations, basic review of higher cognitive concerns and milestones, and appreciating facial dysmorphisms can empower the ophthalmologist to independently suspect genetic disorders in time [Fig. 3]. Among these, the elicitation of family history is a simple, inexpensive, and quick method to suspect genetics early.<sup>[11]</sup> There are multiple online pedigree tools available at the disposal of the Internet to guide the ophthalmologist. Interestingly, artificial intelligence-based tools like facial dysmorphology novel analysis (FDNA, <sup>FACE2GENE</sup>) can also be an aid to guide the ophthalmologist in order to suspect genetics when faced with a “dysmorphic” phenotype.<sup>[12]</sup>

One of the useful tools in the regard of early suspicion of genetics is the mnemonic, “Family GENES.”<sup>[13]</sup> This *aide-mémoire* suggests the following to be early alerts for any underlying genetic concern: family history (similar complaints in parents/siblings/multiple individuals in the same family), group of congenital anomalies (e.g., ocular features in association with major malformations like cleft lip/cleft palate/congenital heart disease or minor malformations like clinodactyly, simian crease), extreme or exceptional presentation of common conditions (e.g., extremely high myopia), neurodevelopmental delays and regression (e.g., Down syndrome), extreme or exceptional pathology (e.g., congenital glaucoma), and surprising laboratory values (very low/absent low-density lipoprotein [LDL]-cholesterol levels in an adolescent with progressive deterioration of night vision and atypical retinal pigmentation could suggest the possibility of *APOB*-related abetalipoproteinemia, a potentially treatable condition if detected early).<sup>[14]</sup>

The current study has limitations of a small sample size, possible over-referral bias among both groups, as well as lack of confirmation prospectively as to how many cases suspected truly turned out to have an underlying genetic disorder. However, it is a first-of-its-kind study designed in India, primarily to understand the referral practice efficiency among pediatric ophthalmologists in an urban set-up in India. This study will hopefully stimulate more research in this direction and help us design systematic and high-yield training modules aimed to better sensitize ophthalmologists toward genetic disorders.

## Conclusion

The study identifies the lacunae in genetic referral pattern amongst pediatric ophthalmologists. It emphasizes on the common clinical red flags which can help suspect genetic disorders early.

### Contribution of each author

SB, MV, and NA were involved in collecting patient data and conducting literature search. SB, MV, NA, and MK were involved in the primary conceptualization of the manuscript and revising it for scientific content. SB will act as the guarantor of the paper.

The manuscript has been read and approved by all the authors, the requirements for authorship have been met, and each author believes that the manuscript represents honest work.

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### Conflicts of interest

There are no conflicts of interest.

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