Review Article

Retinoblastoma genetics in India: From research to implementation

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Retinoblastoma is the prototypic genetic cancer. India carries the biggest burden of retinoblastoma globally, with an estimated 1500 new cases annually. Recent advances in retinoblastoma genetics are reviewed, focusing specifically on information with clinical significance to patients. The Indian literature on retinoblastoma clinical genetics is also highlighted, with a comment on challenges and future directions. The review concludes with recommendations to help clinicians implement and translate retinoblastoma genetics to their practice.

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Introduction

As the first tumor to be confirmed to have genetic origins,[1-5] the study of retinoblastoma has contributed much to our understanding of heritability of cancer. While most of the genetic research aims to elucidate the precise molecular development of the disease, there are important discoveries that can be applied directly to patient care and improve lives.

An estimated 20% of the world's retinoblastoma patients live in India. This has great implications for India's healthcare system, not only in the burden it creates, but the opportunities that emerge for the health and research.

This review article has two main aims. First, it reviews advances in retinoblastoma genetics, specifically focusing on information that is currently relevant and applicable to patient care. Second, it presents a scoping review aimed at determining the breadth and depth of retinoblastoma clinical genetic work in India. The review article concludes with recommendations to help healthcare workers implement and translate retinoblastoma genetics in their clinic so that Indian families affected with retinoblastoma can benefit from the most up-to-date relevant science.

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Methods

Search strategy 1

Review of retinoblastoma clinical genetics

To inform the first part of this review, a search of PubMed (accessed January 15, 2014) was performed to identify relevant and timely articles. Key words included "retinoblastoma genetics," "*RB1* gene," "retinoblastoma genetic testing," and "retinoblastoma genetics counseling." Additional reviews on retinoblastoma and retinoblastoma genetics were identified by hand-searching.

Search strategy 2

Scoping review of Indian retinoblastoma clinical genetics

To inform the second part of this review article, PubMed was searched (January 15, 2014) for all articles that listed "retinoblastoma' " as a key word and "India" as an affiliation. Results of the search were exported as a. comma separated value (.csv) file and analyzed using Microsoft Excel.

Study selection, inclusion and exclusion criteria

Papers that did not explicitly focus on retinoblastoma were excluded. Papers were coded as "Clinical" (primary research on patients and/or patient outcomes), "Basic" (primary research relating to biological mechanisms of retinoblastoma), "Genetic" (primary research relating to retinoblastoma medical genetics/mutation detection) or "Review" (nonprimary research, review articles). A Google Search with the terms "retinoblastoma genetics in India" was also performed (January 21, 2014), in order to locate additional clinical genetics papers that might have been missed in the PubMed search.

Data extraction and analysis

Where provided, data were extracted from clinical genetics papers to calculate the sensitivity of *RB1* mutation testing

for unilateral (UNI) and bilateral (BI) cases. This information included: Number of patients reported on, laterality, number of blood specimens tested (BI), number of M1 mutations found (BI), number of tumor specimens tested (UNI), number of M1/M2 pairs of mutations found (UNI).

Retinoblastoma genetics: An overview

Genetic origins and heritability of retinoblastoma

Retinoblastoma was the first tumor in which the genetic nature of cancer was revealed.[1-5] Even though all retinoblastoma tumors are caused by genetic aberrations, this does not mean that all patients have inherited the disease, nor does it mean that all cases are heritable by the next generation. More recent studies also show us that retinoblastoma tumors may differ in the mutagenic pathway they take from normal to malignant cell; for example, some retinoblastoma tumors are caused by *RB1* mutation[1-5] and others by amplification of the *MYCN* gene.[6] To understand retinoblastoma genetics, it is helpful to think of the disease in terms of heritability (heritable or nonheritable) and laterality (UNI or BI).

Individuals with heritable retinoblastoma (48%) carry a germline mutation in the *RB1* tumor suppressor gene, and are predisposed to developing not just retinal tumors (UNI, 7%, or BI, 40%), but also pineal tumors (trilateral) and second cancers later in life. The majority of heritable retinoblastoma patients will develop retinal tumors, either benign (retinoma) or malignant (retinoblastoma) both caused by loss of the second *RB1* allele in a susceptible retinal cell. However, it is also possible to have heritable retinoblastoma and develop no retinal tumors (1%); these individuals are still at risk for cancers later in life [Fig. 1].[7]

Approximately, 10% of individuals with heritable retinoblastoma will have inherited the *RB1* mutation from a parent. This means the majority of individuals with heritable retinoblastoma are the first affected person in their family.

Approximately, 4% of individuals with heritable retinoblastoma are mosaic for the *RB1* mutation, meaning that the mutation occurred during embryogenesis and affects a fraction of the total germline.[8,9] Mosaic individuals could not have inherited their mutation (otherwise they would carry the *RB1* mutation in all of their cells) but their disease could be heritable by the next generation. Arguably, mosaicism may reduce the risk of transmission for the next generation; however, there exist no reliable data at the moment to be able to accurately calculate potential reduced risks.

Individuals with nonheritable retinoblastoma (52%) have normal *RB1* genes at the germline level. Tumors are always UNI and unifocal, and develop in one of two ways: (1) Loss of both copies of *RB1* in a susceptible retinal cell (51%), or (2) amplification of the *MYCN* oncogene in a susceptible retinal cell (1%). Since the genetic aberrations are somatic, these individuals are not at increased risk for cancers later in life, nor are any of their relatives, present or future.[7]

Genetic progression of retinoblastoma

For the majority of retinoblastoma tumors, the loss of two *RB1* alleles in a susceptible retinal cell induces genomic instability that leads to copy number alterations in several other genes: Copy number gains in *MDM4*, *KIF14*, *MYCN*, *DEK*, and *E2F3*, as well as loss of *CDH11*.[10] The relative degree of gains and losses distinguishes benign retinoma (less genomic instability) from malignant retinoblastoma (more genomic instability).[11] Additional genetic alterations during the development of retinoblastoma include deregulation of microRNAs, aberrant methylations, single nucleotide polymorphisms, and differential gene expression; these have been comprehensively reviewed elsewhere.[12]

Less is known about the development of the $MYCN^{amp}$ tumors beyond the initiating amplification of the *MYCN* oncogene.[6] Is *MYCN* amplification the only genomic event driving malignancy of these tumors? Do $MYCN^{amp}$ tumors have a different cell of origin than *RB1*−/− retinoblastomas? These questions remain to be answered, and further study is required.

Retinoblastoma genetic testing and counseling

With respect to the retinoblastoma patient, while research into the genetic progression of retinoblastoma beyond the initiating mutational event may one day lead to targeted therapies, today, very little of this work is relevant to clinical care. Instead, it is imperative to know whether or not they have heritable retinoblastoma; additional information on the identity of the initiating event can then be used to direct care. For example, it is obvious that all BI patients have heritable retinoblastoma, however, without genetic testing to discover the identity of the *RB1* mutation, precise prediction of risk in family members and future offspring is not possible. This becomes even more important for UNI patients, where precise genetic detection can differentiate between heritable and nonheritable cases, and *RB1*−/− versus $MYCN^{amp}$ retinoblastoma.

Knowledge of the molecular genetic make-up of retinoblastoma tumors and an individual's mutation carrier status makes surveillance and treatment of the patient and related families possible, while elimination of this risk excludes individuals from unnecessary hospital visits and worry. For this to happen, two tools are important: Comprehensive genetic testing by a capable lab and sensitive and accurate counseling to relay the information to the patient and family.

Retinoblastoma genetic testing

The discovery and interpretation of the genetic result are only as good as the technique that precedes it. This starts from the point of the sample (blood and/or tumor) collection. This is particularly important for tumor, which unlike blood, can only be sampled once: after enucleation and before the rest of the eye is sent to histopathology. A protocol has been suggested to optimize tumor collection for genetics while maintaining the integrity of the specimen for subsequent histopathological analysis.[13] The choice of storage media is important so as to ensure optimal extraction of DNA, and possibly RNA. Laboratories that specialize in retinoblastoma genetics can advise on the optimal collection, storage and transport procedures for both tumor and blood.

RB1 testing

Virtually, every new retinoblastoma patient will display a unique *RB1* mutation (excluding of course, those who have $MYCN^{amp}$ retinoblastoma).[14,15] Very few *RB1* mutations are recurrent. This means that genetic testing in the proband is always a journey of discovery, rather than a simple screen for known mutations. The *RB1* gene can be damaged in a

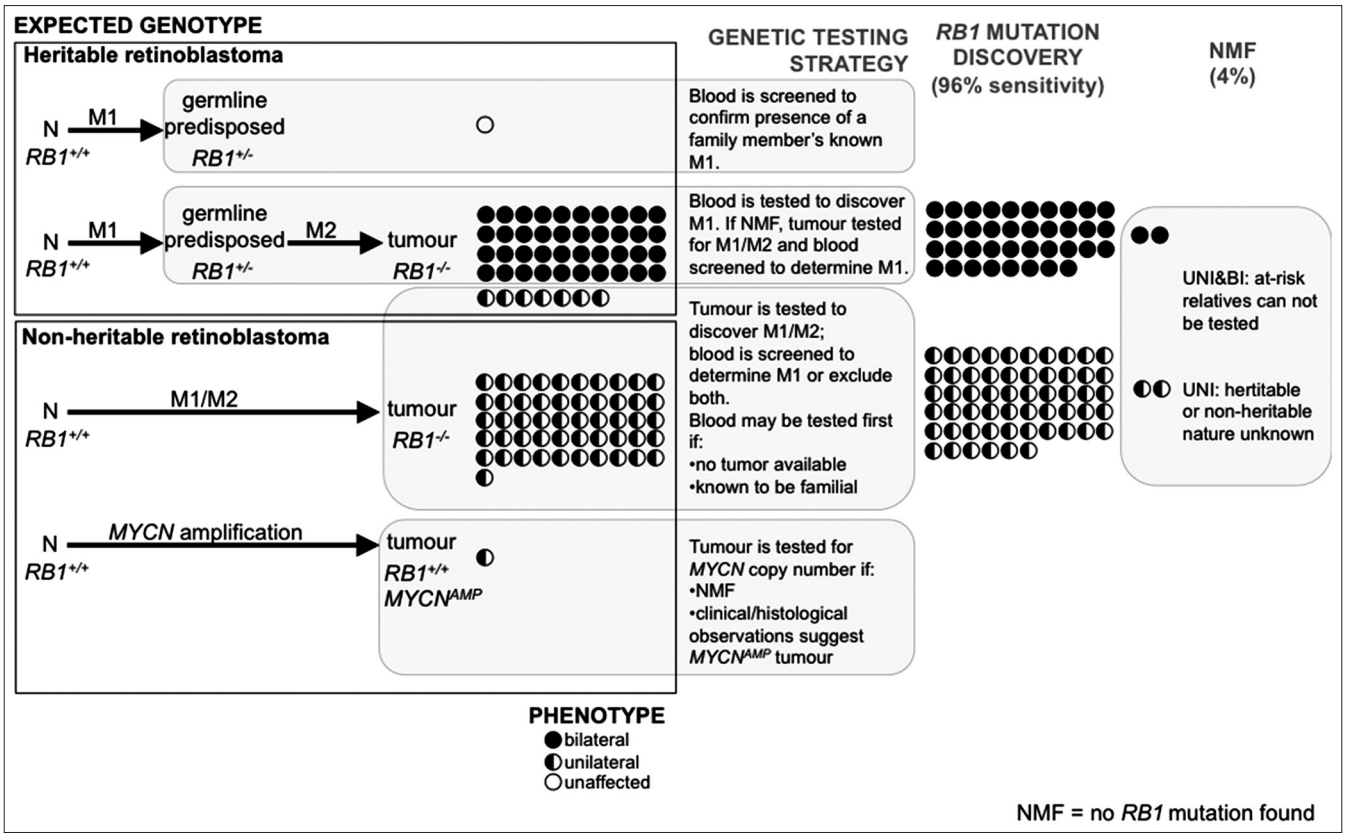

Figure 1: Retinoblastoma genetics overview. In a population of 100 people with a retinoblastoma phenotype or genotype, we expect 1 unaffected (no eye tumor), 40 bilateral, and 59 unilateral cases. Of these, the unaffected and bilateral cases will have heritable retinoblastoma, with an *RB1* mutation detectable in blood. We expect 7 unilateral cases to also carry an *RB1* mutation in the blood while 51 will be nonheritable somatic cases where both *RB1* mutations have occurred in the tumor alone. We expect 1 nonheritable unilateral case to have a normal *RB1* gene in blood and tumor, the retinoblastoma having been initiated by amplification of the *MYCN* gene. The genetic testing strategy for each category is described

myriad of ways, including large and small deletions, point mutations, insertions, translocations, deep intronic splice mutations, and promoter methylation.[14,15] This means many different techniques must be used in the search of the offending mutation.[15-17] However, once the exact mutation is identified in the proband, then relatives and future offspring can be screened quite easily for the known mutation.

Test sensitivity

There are several laboratories around the world that offer retinoblastoma genetic testing services, ranging from fully certified commercial diagnostic labs to basic science research labs. Test sensitivity can be one way to distinguish how reliable the results are from any one of these laboratories.

Test sensitivity is calculated separately for UNI and BI cases, using a simple formula:

$$\text{Bilateral Sensitivity} = \frac{\text{No. of germline mutations found (blood)}}{\text{No. of probands tested}}$$

$$\text{Unilateral Sensitivity} = \frac{\text{No. of both mutations found (tumor)}}{\text{No. of probands tested}}$$

Note that for both formulas, we know that the maximum possible outcome is 100%. That is to say, it is known that 100% of BI patients carry a germline *RB1* mutation in the blood; also, it is known that 100% of UNI patients (save for $MYCN^{amp}$ cases) will have mutations in both tumor *RB1* alleles.

This is not to say laboratories should be expected to reach 100% sensitivity. That may well be impossible with currently available methods and technologies. However, the degree of deviation from 100% sensitivity can be used to gauge how well a given laboratory performs in detecting expected *RB1* mutations.

Test sensitivity is an important factor in interpreting a "no mutation found" result. How can one know if a "no mutation found" result is due to limitations of the lab to detect an existing mutation, or if the person being tested is actually not a mutation carrier?

Consider a UNI patient with no family history. Without genetic testing to confirm or eliminate the possibility that this is heritable retinoblastoma, the physician must continue to examine that child in case they develop tumors in the unaffected eye. The child's family members must also be presumed to be at risk.

Now, imagine that the tumor and blood of that child are tested. In the best case scenario, two *RB1* mutations are found in the tumor and then screened for in the blood to determine if the child has heritable (one of the two tumor *RB1* mutations is detected in the blood) or nonheritable retinoblastoma (none of the two tumor *RB1* mutations is detected in the blood).

Alternatively, imagine that the laboratory is sent only a blood sample because the physician has chosen to treat the affected eye (thus no tumor sample is available). The blood sample is tested, but no mutation is found. Is the child truly a nonheritable case, or has the laboratory failed to detect an existing germline *RB1* mutation?

One recommendation that has emerged from the Canadian Guidelines for Retinoblastoma Care states "as long as the laboratory has demonstrated, that 90% of *RB1* mutations can be identified, a negative result means risks are low enough that examinations under anaesthesia can be avoided."[18] Further to this, the number of tumors a given lab has tested also plays a role in interpreting sensitivity. A high sensitivity with very few specimens ever tested is not reliable, in the same way that many specimens tested with a low sensitivity points to limited ability to reliably detect *RB1* mutations. The highest reported sensitivity for *RB1* mutation testing is 96%.[9]

MYCN^{amp} detection

The discovery of *MYCN*^{amp} retinoblastoma is relatively new.[6] A relatively simple copy number test of tumor DNA for the *MYCN* gene can detect this form or retinoblastoma quite easily. Because of its rarity, it makes sense that this test would be performed after genetic testing for *RB1* failed to reveal a mutation in a UNI tumor, or if histology first revealed presence of neuroblastoma-like histology, a distinctive feature of *MYCN*^{amp} retinoblastoma.

Molecular metastatic surveillance

The molecular signature of retinoblastoma tumors can be used to develop individualized genetic screens for surveillance of minimal residual disease or disseminated retinoblastoma. While the standard of care remains morphological detection of disseminated cancer cells by cytology, studies in limited patients have shown that molecular detection might be more the more sensitive approach.[19,20] For UNI nonheritable (*RB1*-initiated) retinoblastoma cases, either of the tumor *RB1* mutations can be used to detect disseminated cancer.[20] For heritable cases, the M2 (nonconstitutional) *RB1* mutation can be used instead.[20] Furthermore, copy-number analysis of any of the post-*RB1* loss genetic events that occur in the tumor,[19] or even *MYCN* for *MYCN*^{amp} tumors, can be used as markers for molecular surveillance. Gene expression of GD2 synthase has also been studied as a molecular marker for disseminated retinoblastoma.[21] Further research remains to be done to support the routine implementation of molecular surveillance into practice.

Retinoblastoma genetic counseling

If complex genetic information is difficult for even the most seasoned of clinicians to understand, then the task of disseminating these findings to patient families becomes even more difficult. In some settings (mainly Europe and North America), genetic counselors may assist in educating patient families about retinoblastoma genetics. In many places around the world, however, this task is often left to the discretion of the treating physician. Recommendations for counseling in the presence and absence of retinoblastoma genetic testing are available,[18] however, it is becoming increasingly clear that the counseling approach may be influenced by context.[22-25] Further research is necessary to develop services that take into account the unique sociocultural context of the setting in question.[26] As advances genomic approaches lead the way forward to individualized medicine, it is important to study how well the medical community and public is equipped to understand the essential genetic concepts that facilitate informed consent, care, and follow-up. These approaches too will vary worldwide.

Retinoblastoma genetics in India – scoping review

Study sample

A search of PubMed for the keyword "retinoblastoma" with author affiliations in India yielded 270 citations [Supplementary File]. Excluding studies that were not exclusively focused on retinoblastoma (114), 156 remained. Of these, the 86 (55%) were clinical studies, 50 (32%) basic science, 14 (9%) clinical genetics, and 6 (4%) reviews [Fig. 2]. The Google search did not yield any additional clinical genetics publications that fit our criteria.

Indian research on retinoblastoma genetics

The 14 retinoblastoma clinical genetics studies came from four centers in India, covering a period of the publication from 2001 to 2011 [Table 1]. Full-text copies of only 13/14 publications could be located, thus 1 publication was excluded from the study [Table 1, Fig. 2].

The purpose of the studies ranged from reporting on the results of comprehensive molecular *RB1* testing (6), evaluation of a specific methodology for *RB1* testing (4), correlating molecular *RB1* result to functional consequence on *RB1* (2) and evaluating cost-effectiveness of molecular testing (1) [Table 1]. Many studies included commentary about the discovery of new *RB1* mutations. No studies reported on the genetic counseling or general implementation of molecular genetic testing into clinical practice in India.

Only 4/6 studies reporting *RB1* mutation discovery (representing 2 institutions) provided enough data such that the sensitivity of BI and UNI testing could be determined [Table 2]. Where data were provided, BI and UNI

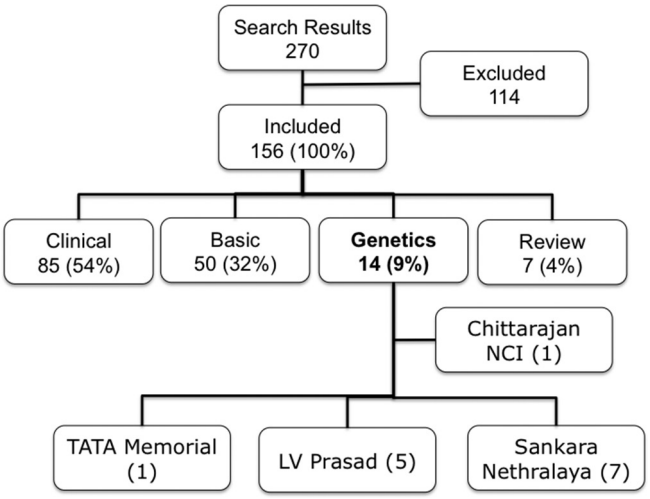

Figure 2: Scoping review flow diagram. A search of PubMed for the keyword "retinoblastoma" with author affiliations in India yielded 270 citations. Excluding studies that were not exclusively focused on retinoblastoma (114), 156 remained. Of these, the 86 (55%) were clinical studies, 50 (32%) basic science, 14 (9%) genetics, and 6 (4%) reviews. Full-text articles were located for 13/14 of the genetics publications, as illustrated

Table 1: List of clinical genetics articles published in India

Number	Title	Authors	Journal	Year	Purpose	Institute	Sensitivity data
1	Prediction of retinoblastoma and osteosarcoma: Linkage analysis of families by using polymorphic markers around *RB1* locus	Chunder N, Basu D, Roy A, Roychoudhury S, Panda CK	J BUON	2003	Excluded; no full text available	Chitarranjan National Cancer Institute	NA
2	Mutational analysis of the *RB1* gene in Indian patients with retinoblastoma	Ata-ur-Rasheed M, Vemuganti GK, Honavar SG, Ahmed N, Hasnain SE, Kannabiran C	Ophthalmic Genet	2002	Comprehensive *RB1* mutation testing	LV Prasad	Yes
3	Mutational screening of the *RB1* gene in Indian patients with retinoblastoma reveals eight novel and several recurrent mutations	Kiran VS, Kannabiran C, Chakravarthi K, Vemuganti GK, Honavar SG	Hum Mutat	2003	Comprehensive *RB1* mutation testing	LV Prasad	Yes
4	A comprehensive, sensitive and economical approach for the detection of mutations in the *RB1* gene in retinoblastoma	Parsam VL, Kannabiran C, Honavar S, Vemuganti GK, Ali MJ	J Genet	2009	Comprehensive *RB1* mutation testing	LV Prasad	Yes
5	*RB1* gene mutations in retinoblastoma and its clinical correlation	Ali MJ, Parsam VL, Honavar SG, Kannabiran C, Vemuganti GK, Reddy VA	Saudi J Ophthalmol	2010	Functional consequence of *RB1* mutation	LV Prasad	NA
6	Splicing aberrations caused by constitutional *RB1* gene mutations in retinoblastoma	Parsam VL, Ali MJ, Honavar SG, Vemuganti GK, Kannabiran C	J Biosci	2011	Functional consequence of *RB1* mutation	LV Prasad	NA
7	Genetic profile of 81 retinoblastoma patients from a referral hospital in southern India	Harini R, Ata-ur-Rasheed M, Shanmugam MP, Amali J, Das D, Kumaramanickavel G	Indian J Ophthalmol	2001	Evaluation of specific methodology (cytogenetics)	Sankara Nethralaya	NA
8	Molecular-genetic analysis of two cases with retinoblastoma: Benefits for disease management	Kumaramanickavel G, Joseph B, Narayana K, Natesh S, Mamatha G, Shanmugam MP, Elamparathi A, Biswas J	J Genet	2003	Comprehensive *RB1* mutation testing	Sankara Nethralaya	Incomplete
9	Methylation status of *RB1* promoter in Indian retinoblastoma patients	Joseph B, Mamatha G, Raman G, Shanmugam MP, Kumaramanickavel G	Cancer Biol Ther	2004	Evaluation of specific methodology (methylation)	Sankara Nethralaya	NA
10	Retinoblastoma: Genetic testing versus conventional clinical screening in India	Joseph B, Shanmugam MP, Srinivasan MK, Kumaramanickavel G	Mol Diagn	2004	Cost-effectiveness of *RB1* mutation testing	Sankara Nethralaya	NA
11	Karyotyping in retinoblastoma-a statistical approach	Joseph B, Paul PG, Elamparithi A, Roy J, Vidhya A, Shanmugam MP, Kumaramanickavel G	Asian Pac J Cancer Prev	2005	Evaluation of specific methodology (karyotype)	Sankara Nethralaya	NA

Contd...

Table 1: Contd...

Number	Title	Authors	Journal	Year	Purpose	Institute	Sensitivity data
12	Genotype-phenotype correlation analysis in retinoblastoma patients from India	Joseph B, Raman R, Uthra S, Jagadeesan M, Ganesh A, Paul PG, Sharma T, Kumaramanickavel G	Asian Pac J Cancer Prev	2006	Comprehensive *RB1* mutation testing	Sankara Nethralaya	Incomplete
13	Retinoblastoma in India: Microsatellite analysis and its application in genetic counseling	Ramprasad VL, Madhavan J, Murugan S, Sujatha J, Suresh S, Sharma T, Kumaramanickavel G	Mol Diagn Ther	2007	Evaluation of specific methodology (LOH and microsatellite)	Sankara Nethralaya	NA
14	Constitutional and somatic *RB1* mutation spectrum in nonfamilial UNI and BI retinoblastoma in India	Bamne MN, Ghule PN, Jose J, Banavali SD, Kurkure PA, Amare Kadam PS	Genet Test	2005	Comprehensive *RB1* mutation testing	TATA Memorial	Yes

LOH: Loss of heterozygosity, NA: Not available, BI: Bilateral, UNI: Unilateral

sensitivity ranged in reports from the same institutions, an overall sensitivity of combined cases from that one center was calculated. BI sensitivity ranged from 36% to 75%, and UNI sensitivity ranged from 26% to 35% [Table 2]. Table 2 provides more details on number of specimens tested by each laboratory in their respective reports.

Way forward

The main purpose of this article was to review the current knowledge of retinoblastoma genetics as it relates to patient care, and juxtapose that alongside published evidence of retinoblastoma genetic testing as it is implemented in India.

Is genetic testing part of the standard of care for retinoblastoma in India? While certainly there exist laboratories that provide retinoblastoma genetic testing, this review did not consider possible barriers (social, economic, etc.) that may prevent a family from benefiting from the service. That some families may access retinoblastoma testing from international laboratories was also not considered. The review also did not consider institutional or logistical limitations that may prevent a laboratory from achieving reliable, high-quality results, nor were nonacademic publications from commercial labs that might offer retinoblastoma genetic testing surveyed. However, this review of academic research on retinoblastoma genetics within the Indian context does suggest the existence of a "know-do" gap: The current knowledge of retinoblastoma genetics does not appear to be implemented comprehensively in India. While a handful of laboratories in India have published their experience with *RB1* genetic testing, the quality of reports varies, and it is difficult to ascertain how reliable testing is from different institutions [Table 2]. For the practicing physician caring for retinoblastoma children, reliability of results is imperative, as it affects their choice of subsequent treatment and surveillance plan.

One major concern that emerged from looking at reports of molecular testing for retinoblastoma is that test sensitivity is not consistently reported. Often an overall sensitivity for BI and UNI cases was reported, and the sensitivity reported in this paper had to be calculated with the raw data – and in some cases, this raw data was not reported. Test sensitivity is important information that every retinoblastoma practitioner must arm themselves with in order to practically interpret the results of a given report.

A low test sensitivity does not necessarily mean that a given laboratory should be avoided; rather, an honest account of the sensitivity allows for an educated decision after a "no mutation found" result if it is used to conduct genetic testing. For example, one of the centers in this review had a sensitivity of 83% for BI cases in their more recent publication [Table 2].[4] A physician receiving a "no mutation found" result from this laboratory may wish to have the specimen re-tested by a lab with a higher sensitivity. There are many innovative approaches to be explored, not just for laboratories to improve their own sensitivity, but for physicians who order these tests to maximize use of available resources and get the results they need for their patients.

While sensitivity appears to be ignored or inadequately calculated in some reports, despite its clinical importance, it is striking to see how often novel *RB1* mutations are reported in the literature. It is well known that the *RB1* gene can be

Table 2: *RB1* mutation detection sensitivity

Number	Institution	Number of patients	BI sensitivity				UNI sensitivity			
			Number of BI patients	Number of BI blood studied	Number of M1 found	BI sensitivity (%)	Number of UNI patients	Number of UNI tumors studied	Number of UNI M1/ M2 found	UNI sensitivity (%)
2	LV Prasad	21	12	12	5	42	9	2	2	100
3	LV Prasad	47	32	20	15	75	15	15	4	27
4	LV Prasad	74	53	53	44	83	21	0	NA	NA
					Overall	75			Overall	35
14	TATA Memorial	34	11	11	4	36	23	23	6	26

BI: Bilateral, UNI: Unilateral, M1: First *RB1* mutation, M2: Second *RB1* mutation, NA: Not available

damaged in any number of ways – new types of mutations are the norm for retinoblastoma, and rarely result in novel clinical significance to the patient. Perhaps it is time to re-examine the focus of retinoblastoma genetics research. For example, increasing a laboratory's capability to find all existing *RB1* mutations (i.e. improving sensitivity) through novel approaches is a significant finding; finding a new way that the *RB1* gene can be potentially damaged (while failing to detect the majority of *RB1* mutations in other patients), is not.

Much like the rest of the world, the Indian research focus for retinoblastoma centers around clinical and basic science, with little focus on clinical genetics or its implementation into practice [Fig. 2, Supplementary File]. However, India is in the unique position of carrying the highest burden of retinoblastoma in the world.[27] There is much more to be gleaned in this context to bridge the retinoblastoma genetics "know-do" gap. This new information and knowledge, once generated, could have vast utility for the global retinoblastoma population. There is no shortage of Indian intellect and people-power to produce groundbreaking research and new knowledge. Particularly, in this current era of genomic advances, there is much to be done for the benefit of Indian children with retinoblastoma, and by default the rest of the world. Still, the literature does not seem to indicate this power is being harnessed just yet. With a careful, evidence-based approach, India can rise to its potential and be a leader in the next wave of genetic research and care for retinoblastoma.

Supplementary File: Detailed list of all 270 citations resulting from PubMed Search.

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