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The history of human cytogenetics in India—A review

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ABSTRACT

It is 60 years since the discovery of the correct number of chromosomes in 1956; the field of cytogenetics had evolved. The late evolution of this field with respect to other fields is primarily due to the underdevelopment of lenses and imaging techniques. With the advent of the new technologies, especially automation and evolution of advanced compound microscopes, cytogenetics drastically leaped further to greater heights. This review describes the historic events that had led to the development of human cytogenetics with a special attention about the history of cytogenetics in India, its present status, and future. Apparently, this review provides a brief account into the insights of the early laboratory establishments, funding, and the German collaborations. The details of the Indian cytogeneticists establishing their labs, promoting the field, and offering the chromosomal diagnostic services are described. The detailed study of chromosomes helps in increasing the knowledge of the chromosome structure and function. The delineation of the chromosomal rearrangements using cytogenetics and molecular cytogenetic techniques pays way in identifying the molecular mechanisms involved in the chromosomal rearrangement. Although molecular cytogenetics is greatly developing, the conventional cytogenetics still remains the gold standard in the diagnosis of various numerical chromosomal aberrations and a few structural aberrations. The history of cytogenetics and its importance even in the era of molecular cytogenetics are discussed.

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1. Introduction

The beginning of human cytogenetics started with Walther Flemming, an Austrian cytologist and professor of anatomy, who published the first illustrations of human chromosome in 1882 (Flemming, 1882). Then, Theodar Boveri who is known as the "first genetic engineer" worked on chromosome structure and function and also suggested that the abnormalities in mitotic polarity could be caused by an abnormal number of centromeres which established the asymmetrical segregation of chromosomes (Boveri, 1914; Harris, 2008). Later on, Sutton and Boveri developed the "chromosome theory of inheritance" (Sutton, 1903; Boveri, 1902). It was Sutton who had combined the two disciplines of cytology and genetics which he referred as cytogenetics, the study of chromosomes.

Initially, there is no specific field of human cytogenetics. It was the plant geneticists who had pioneered the techniques and only in 1940s the progress started. The reason for the slow progress can be attributed to the underdevelopment of lenses and imaging techniques. Finally, with the advancement of glass, i.e., lenses, the development of cytogenetics progressed. Cytogenetics is now defined as the study of structure, function, and evolution of chromosomes.

Abbreviations: GTG-banding, G-banding using Trypsin and Giemsa; NOR, Nucleolar organizing regions; R-banding, Reverse Giemsa banding; Q-banding, Banding with fluorescent quinacrine mustard stain; C, Centromere banding.

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Here the history of human cytogenetics in India along with German collaborations is detailed and discussed. This review is by no means exhaustive, but rather a small attempt to reveal the major landmarks that have aided in the advancement of the human cytogenetics in India.

1.1. Milestones in cytogenetics

The term karyotyping is coined by Heinrich W. G. von Waldeyer-Hartz in 1888. The first report of Giemsa stain was published way back in 1904, and Giemsa was selected for staining the chromosomes as it is a mixture of azure B, eosin, and methylene blue dyes, which attaches to the phosphate groups at the adenine–thymine bonds of DNA. The birth of modern human cytogenetics occurred with the discovery of 46 chromosomes in a diploid cell by Joe Hin Tjio while visiting the Institute of Genetics at the University of Lund in Sweden in 1955. Tjio along with Albert Levan carried out work on human embryonic cells and in 1956 published the correct number of chromosomes (Tijo and Levan, 1956). These studies were confirmed on testicular material by Ford and Hamerton (Ford et al., 1956). The important milestone in the history of cytogenetics is the discovery of use of the hypotonic solution for chromosome spreading procedures independently by Hsu, Makino, and Hughes in 1952 (Hsu, 1952; Hsu et al., 1953; Makino and Nishimura, 1952; Hughes, 1952). In April 1952, Hsu discovered a technique that separated the clumped chromosomes, thereby allowing him to observe each chromosome individually. In fact, Hsu is considered as father of mammalian cytogenetics. Yet another important finding is

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the addition of colchicine to cell cultures, which destroys the mitotic spindle fibers, and subsequently, the cells do not enter the anaphase stage and hence unable to complete the mitosis. As a result, large numbers of metaphase cells are retained and available for microscopy (Ford and Hamerton, 1956). The chromosomes were later improved by the use of phytohemagglutinin stimulation (Moorhead et al., 1960).

1.2. Modern human cytogenetics and the eras

Based on technologies, the modern human cytogenetics is classified into three eras. Each era showed a significant development which helped in the progress of cytogenetics.

1. *The Golden Era (1950–1970)*

It was in this era that the exact number of chromosomes was discovered followed by the introduction of methodologies for chromosome preparations. During this period, various tissues were experimented and the importance of peripheral blood as a source for chromosome analysis was identified.

2. *Era of Banding (1970–1980)*

The second era brought a revolution in cytogenetics and is marked as one of the innovative era. Several banding techniques were developed which made the easy identification of individual chromosomes. The banding techniques unraveled the chromosomes in detail when compared to the simple staining techniques with Giemsa (Fig. 1). The first type of banding was reported by Caspersson et al. using fluorescence dye quinacrine which showed a banding pattern. This enabled the recognition of every single chromosome and thus Q-banding was identified (Caspersson et al., 1970). Later, Seabright (1971), using trypsin, was able to obtain a characteristic G-band. This showed better resolution than Q-bands as it allowed permanent preparations and avoided the use of fluorescence microscope. Hence, G-banding paved way for the modern international classification of chromosomes (ISCN, 1985).

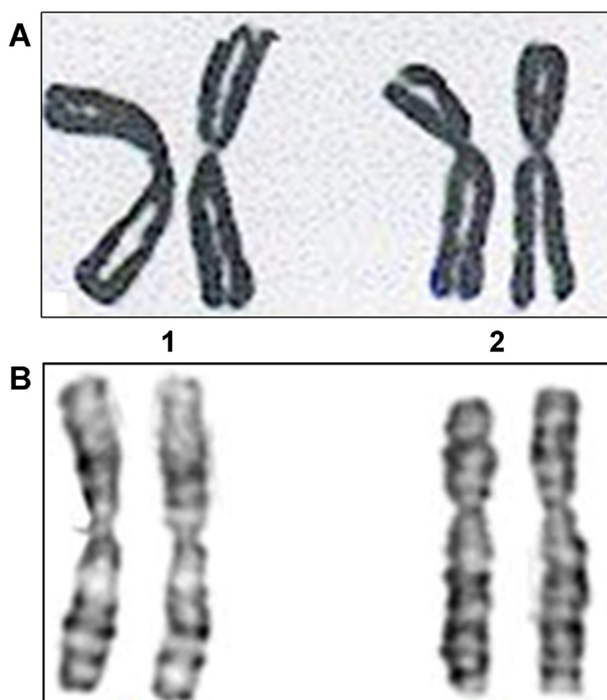

Fig. 1. The comparison of chromosomes with Giemsa staining and G-banding. *A*: Partial metaphase showing chromosome 1 and 2 with only Giemsa stain. *B*: GTG-banding showing the G-bands on chromosomes 1 and 2.

Later on, another technique called C-banding derived from centromeric or constitutive heterochromatin was discovered by Mary L. Pardue and Joseph G. Gall as a byproduct of the *in situ* RNA/DNA hybridization (Pardue and Gall, 1970). The labeled probes hybridized to distinct regions of each chromosome next to the centromere were referred to as the centromeric or pericentromeric heterochromatin. With this background subsequently, a Giemsa staining procedure without the use of radio-labeled probes was described by Sumner. This preferentially stains centromeric heterochromatin and is widely used C-banding technique now (Sumner et al., 1971).

Several other banding techniques were also developed like Reverse Giemsa banding (RGB) and Nucleolar organizing region (NOR) staining, each having its own specific properties and applications (Rooney, 2001). For instance, in RGB, the R-banding produces bands complementary to G-bands, which are induced by the action of hot phosphate buffer and stained with Giemsa (Dutrillaux and Lejeune, 1971). The NOR staining is a technique that stains NORs of acrocentric chromosomes (Matsui et al., 1973). These regions are located in the satellite stalks of acrocentric chromosomes which house the genes for ribosomal RNA. This technique was developed by Goodpasture to study the double satellites (Goodpasture et al., 1976; Goodpasture et al., 1975). Apparently, for routine analysis, the G-banding technique using trypsin and Giemsa became the most accepted worldwide.

Subsequently, in 1976, Yunis (1976) identified a high-resolution banding method using prometaphase chromosomes that allowed the cytogenetic anomalies to be easily identified. By high-resolution technique, several already well-known clinical syndromes were linked to small chromosome aberrations and the concept of the micro deletion or contiguous gene syndrome was born (Schmickel, 1986). The revolution in banding techniques made it possible for a detailed chromosomal analysis which led to the identification of several other different chromosomal aberrations and the discovery of the new cytogenetic syndromes (Garcia-Sagredo, 2008). Thus, the importance of cytogenetics evolved in clinical applications especially in prenatal diagnosis and cancer cytogenetics.

During this era, many numerical aberrations like Trisomy 21 (Lejeune et al., 1959), 45,X in Turner syndrome (Ford and Hamerton, 1959), 47,XXY in Klinefelter syndrome (Jacobs et al., 1959), Trisomy 13 (Patau et al., 1960), Trisomy 18 (Edwards et al., 1960), and Philadelphia chromosome in a patient with chronic myeloid leukemia (Nowell et al., 1960) were detected. The history of these early events in diagnostic cytogenetics is detailed elsewhere in many reviews (Ferguson-Smith, 1960, 1961, 2012).

The discovery of the exact number of chromosomes had stimulated an interest in human cytogenetics and many labs evolved, in the process a variety of classification also evolved which resulted in utter confusion. Hence, the need to establish a common system of nomenclature has arisen. Apparently, a small group comprising 14 investigators and 3 consultants convened a meeting in Denver, Colorado. The meeting proposed a report titled "A proposed system of nomenclature of Human mitotic chromosome" known as Denver Conference (1960). Subsequently, in 1977, a committee at Stockholm unified various conference reports into "An International System for Human Cytogenetic Nomenclature (1978)," abbreviated as ISCN, which included all major reports of Denver, London, Chicago, and Paris conferences, without any major changes but edited for consistency and accuracy. Apparently, this prevented much of the nomenclature confusion in human cytogenetics and subsequently published as the ISCN nomenclature in 1985, 1995, 2005, 2009, and 2013 which is now followed all over the world.

3. *Era of Molecular Cytogenetics (1980–to date)*

This era is the fusion of conventional cytogenetics with molecular methodologies. Several new techniques like Fluorescence *in situ* Hybridization (FISH) (Fig. 2A), Spectral Karyotyping (SKY) (Fig. 2B), Array

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