

A Review of the Results of Chromosomal Analyses Done at the National Institutes of Health from 1991 to 2007

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ABSTRACT

The Medical Genetics Unit of the University of the Philippines, College of Medicine, which subsequently became the Institute of Human Genetics – National Institutes of Health, University of the Philippines Manila in 1999, houses the Cytogenetics Laboratory that services many hospitals throughout the country through processing of peripheral blood, cord blood, bone marrow and skin/tissue samples for cytogenetic analysis. Bone marrow, cord blood and skin/tissues account for 14.9%, 8.5% and 1.8% of samples analyzed, respectively, and the remainder are peripheral blood (74.8%). This paper presents the results of a retrospective review of the chromosomal analysis done on peripheral blood samples from 1991 to 2007. Of the 10655 samples submitted, 8391 were samples from patients and 2264 were research samples on cytogenetic effects of environmental toxins, (i.e. pesticides, etc.) on high risk populations. Of the 8391 patient samples analyzed, 73.0% were from hospitals in Luzon, 4.0% from Visayas, and 0.9% from Mindanao. Samples from private health practitioners' clinics from different parts of the country accounted for 11.7% of the samples received. There was no information given on source of sample in 10.3%. The top 3 reasons for referral for cytogenetic studies are confirmation of a chromosomal diagnosis, cytogenetic effects of environmental toxins (i.e. pesticides), and recurrent miscarriages/poor obstetric history. Numerical chromosome abnormalities (86.6%) were more common than structural abnormalities (13.39%). Among the numerical abnormalities, 90.2% were autosomal, and Trisomy 21 is the most common type of aneuploidy seen. For sex chromosome abnormalities, the classic form of Turner was most prevalent. Deletions, additions, and translocations were the most predominantly ascertained structural abnormalities of the chromosomes in this review. This paper aims to review the abnormal results of the chromosomal analysis done on peripheral blood samples of patients processed by the Cytogenetics Laboratory of the Institute of Human Genetics from 1991 to 2007. Data of research samples will not be included in this paper.

Key Words: cytogenetics, numerical chromosome abnormalities, structural chromosome abnormalities, sex chromosome abnormalities

Introduction

The field of human cytogenetics is an increasingly important area of medicine as it has helped elucidate the

etiology of many congenital malformation and mental retardation syndromes. It is also used in the field of malignancy to establish the presence of malignant clones, clarify the diagnosis, indicate prognosis, assist with the choice of a treatment strategy, monitor response to treatment and support further research. Various chromosomal abnormalities constitute a substantial proportion of human morbidity and mortality. Among the clinical indications for which cytogenetic analysis is requested include presence of congenital anomalies, mental retardation, disorders of sex differentiation, infertility or recurrent miscarriages, hematologic malignancies and other cancers, prenatal diagnosis, and exposure to radiation and toxic chemicals.¹⁻⁵ Peripheral blood remains the tissue of choice for post natal studies because it is easily available.⁶ Skin/tissue samples can be used for investigation of mosaic karyotypes or detection of abnormalities not normally present in lymphocytes.⁷ Bone marrow is the tissue of choice for cancer cytogenetics.⁸

In 1991, cytogenetics service was started at the Medical Genetics Unit of the University of the Philippines College of Medicine. This unit eventually became the Institute of Human Genetics, National Institutes of Health, University of the Philippines Manila (IHG-NIH-UPM) in 1999.

This paper aims to review the abnormal results of the chromosomal analysis done on peripheral blood samples processed by the Cytogenetics Laboratory of the Institute of Human Genetics from 1991 to 2007. Specifically, this paper aims to determine the major types of chromosomal aberrations and classify them according to standard nomenclature.

Materials and Methods

Results of the chromosomal analysis done on peripheral blood samples from 1991 to 2007 were retrospectively reviewed. Samples were from patients referred by: 1) physicians (pediatricians, obstetricians, hematologist, oncologists, etc) from different government and private hospitals; 2) private health practitioners coming from all over the country; and 3) researchers.

Submitted specimens were processed at the Institute of Human Genetics-National Institutes of Health-University of the Philippines Manila according to established protocols for peripheral blood.⁹ Reporting used the International System for Human Cytogenetic Nomenclature (2005).¹⁰

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Results and Discussion

A total of 10655 peripheral blood samples were submitted to the Cytogenetics Laboratory from 1991 to 2007 by physicians from government/private hospitals and private health practitioners and researchers from all over the country. Of the 10 655 samples, 8391 were patient samples and 2 264 peripheral and cord blood samples were submitted by research groups to identify the cytogenetic effects of environmental toxins (i.e. pesticides). Research data will not be presented in this paper.

Majority of patient samples came from the government/private hospitals – 6127 (73.0%) from Luzon, 337 (4.0%) from Visayas and 76 (0.9%) from Mindanao. Samples from private health practitioners' clinics from different parts of the country accounted for 984 (11.7%) of the samples received. There was no information provided or the location of hospital could not be ascertained in 867 (10.3%) samples. Table 1 shows the leading 10 reasons for referral for cytogenetic studies.

Table 1. Top 10 reasons for referral for cytogenetic study (1991-2007)

Reasons for referral	No. of requests
1. Confirmation of a chromosomal diagnosis	3449
2. Cytogenetic effects of environmental toxins, i.e pesticides	2264*
3. Recurrent miscarriages/poor OB History	973
4. Multiple congenital anomalies	809
5. Possible chromosomal findings in syndromes	679
6. Ambiguous Genitalia/CAH suspect	374
7. Developmental delay	373
8. Parents & siblings of patients with chromosomal aberrations	328
9. Cytogenetic effects of Leukemia	152
10. Hydrops fetalis	59

*results will not be included in this paper

Among the clinically diagnosed chromosomal abnormalities, confirmation of a suspected trisomy in a patient was the most common reason for referral for cytogenetic analysis (Table 2).

Table 2. Top 3 chromosomal diagnosis as reasons for referral for cytogenetic study (1991-2007)

Chromosomal diagnosis	No. of requests
Trisomy	2433
Trisomy 21	2178
Trisomy 18	186
Trisomy 13	69
Turner Syndrome/amenorrhea	432
Fragile X	123

Among the 8391 samples, 2734 (32.6%) had abnormal cytogenetic results, 2532 (30.2%) had normal male karyotype results, 2524 (30.1%) had normal female karyotype results, and 601 (7.2%) samples had no growth which did not allow karyotyping to be performed. Table 3 presents the distribution of abnormal results.

It is interesting to note that of the 2178 requests (Table 2)

Table 3. Distribution of chromosomal abnormalities seen at the Cytogenetics Laboratory, IHG-NIH-UPM (1991-2007)*

Chromosome abnormality	Number of Cases
Numerical	2368
Autosomal abnormalities	2136
Trisomy 21	1858
Full	1640
Mosaic	134
Translocation type	62
Other variation	22
Trisomy 18	228
Full	217
Mosaic	7
Translocation type	1
Other variation	3
Trisomy 13	44
Full	38
Translocation type	3
Mosaic	3
Trisomy 8	1
Trisomy 9	1
Trisomy 11	1
Trisomy 19	1
Monosomy 21	1
Trisomy 22	1
Sex chromosome abnormalities	231
Turner syndrome (45, X)	185
Classic	72
Mosaic with normal cell line	47
Mosaic with i(X)	28
Mosaic with Trisomy X	3
Other variation	35
Klinefelter (47, XXY)	13
Trisomy X	11
Full	10
Mosaic	1
Monosomy Xp	8
48, XXXY	4
49, XXXXY	4
47, XYY	3
Monosomy Xq	2
48, XXYY	1
Triploidy	1
Structural	366
Deletions	112
Terminal	98
Mosaic	12
Interstitial	2
Translocation	99
Two-break	87
Robertsonian	10
Three-break	2
Addition	64
Marker chromosomes	44
Insertions	12
Ring chromosomes	9
Fragile sites	9
Inversions	7
Duplications	4
Derivative chromosomes	3
Isochromosomes	2
Dicentric chromosome	1
Total Number of Cases	2734

* does not include research data and results from bone marrow and solid tissue

for a possible case of Trisomy 21 or Down Syndrome, 85.3% were confirmed to have Trisomy 21, while 14.7% had other diagnoses. Likewise, for Trisomy 13, of the 69 requests, only 44 or 63.8% were confirmed to have Trisomy 13. In contrast to these, there were 186 requests for confirmation of Trisomy 18 but the Cytogenetics Laboratory was able to diagnose 228 cases. These were probably patients presenting with multiple congenital anomalies wherein Trisomy 18 was not the primary consideration. This data lends support to the importance of performing chromosomal studies to resolve diagnosis inasmuch as correct diagnosis is critical for management and prognostication of the patient. Our data from this review of cases show that Full Trisomy 21, Full Trisomy 18 and Full Trisomy 13 were still the most predominant sub-types ascertained, accounting for 88.3% (1640), 95.2% (217) and 86.4% (38) of the respective groups.

Among the different sex chromosome abnormalities, Turner Syndrome was the most commonly seen accounting for 80.1% of the cases with 38.9% of these were the classical Turner syndrome type.

A variety of different structural chromosome rearrangements were described. Rearrangements occurring within a single chromosome included deletions, duplications, isochromosome and ring formation. Rearrangements involving more than one chromosome included translocations, insertions, marker chromosomes and complex rearrangements. Deletions accounted for a third of the cases, followed closely by translocation cases (27.1%) and addition cases (17.5%).

Deletion of the long arm of the Y chromosome (Yq-), short arm of chromosome 5 (5p- or Cri-du-chat syndrome) and long arm of chromosome 18 (18q-) were the most common deletions ascertained accounting for 6.6%, 5.5% and 3.3% of structural chromosome abnormalities, respectively. Translocations involving chromosomes 9 and 22 (Philadelphia chromosome) were identified in 8.2% of cases and Robertsonian translocations [rob(13;14), rob(13;21), rob(14;21), rob(15;21)] were identified in 2.7% of structural chromosome abnormalities. Most of the chromosomal additions were in chromosomes 10, 22 and the Y chromosome. Fragile X and ring chromosome abnormalities involving chromosomes 4, 10, 13, 18 and 21 were identified.

The use of routine chromosomal analysis is limited to the gross structural appearance of the chromosomes. More recent techniques allow precise identification of chromosomes or parts of chromosomes that are beyond the resolution of routine cytogenetics. Fluorescence in situ hybridization (FISH) is one of these newer methods which utilize fluorescently labeled DNA probes to detect or confirm these different gene or structural chromosome abnormalities. Another technique is an array comparative genomic hybridization (CGH) which utilizes mapped DNA sequences in a microarray format as a platform for the detection of chromosomal deletions/duplications. Its advantage over conventional karyotyping includes a higher

resolution and direct mapping of aberrations to the genome sequence.

Conclusion

In conclusion, visible changes in the number or structure of chromosomes form a major category of clinical conditions. They account for a large proportion of all reproductive wastage, congenital malformations, mental retardation and more than 100 identifiable syndromes. Thus, chromosomal analysis is an increasingly important diagnostic procedure in numerous areas of medicine.

This review presents the diverse types of chromosomal abnormalities detected on peripheral blood samples referred to the Institute of Human Genetics, National Institutes of Health, University of the Philippines Manila from government/private hospitals and from private health practitioners for the past sixteen years (1991-2007). Numerical chromosome abnormalities were more common than structural chromosome abnormalities. Full Trisomy 21 was the most common aneuploidy seen. Classic Turner Syndrome was the most frequent sex chromosome abnormality identified. Deletions, additions and translocations were the most common structural chromosome abnormalities ascertained.

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