Scientific Research Publishing

Open Journal of Genetics, 2023, 13, 97-103
https://www.scirp.org/journal/ojgen
ISSN Online: 2162-4461
ISSN Print: 2162-4453

Correlation between Reasons for Prescription and Karyotype Results in Patients Referred for Suspected Chromosomal Abnormalities

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How to cite this paper: Deh, Z.P., Dieth, M.J.A., Coulibaly, Q.D., Bouatinin, M.O.A., Goulai, B.Y.E.B., Okon, A.J.L., Doukouré, B., Diomandé, M.I.J.-M. and Yao, G.V. (2023) Correlation between Reasons for Prescription and Karyotype Results in Patients Referred for Suspected Chromosomal Abnormalities. *Open Journal of Genetics*, **13**, 97-103.
https://doi.org/10.4236/ojgen.2023.132006

Received: March 24, 2023
Accepted: June 24, 2023
Published: June 27, 2023

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Abstract

Karyotype prescription is based on clinical signs (or reasons for karyotype prescription) which are phenotypic manifestations associated with chromosomal abnormalities. The aim of this study was to establish a correspondence between karyotype indications and their results in patients. This was a retrospective study that was carried out in the Histology-Embryology-Cytogenetics laboratory of the University Hospital of Cocody-Abidjan from 2014 to 2019. 58 patient files were identified and included the indication or reason for prescribing a constitutional karyotype and the biological result obtained. An individual data sheet was used to collect the data. 17 reasons for prescription were identified and divided into 2 groups. Sexual ambiguity was the most frequent reason (29.3%). The first group (G1) represented the 10 reasons for which the karyotype results were normal. The second group (G2) corresponded of the 7 motives with normal or abnormal karyotype results. Several anomalies were listed according to these reasons: inversions, mosaics (anomalies of number and structure) and trisomy 21. The last was the most frequent chromosomal anomaly (69.24%). It was found in several reasons for karyotype prescription: malformations, neurological disorders, suspected trisomy and cardiac pathology. Several factors could explain these results, among which are the limits of the karyotype and the non-genetic causes that can induce these abnormal phenotypes. Complementary examinations to the karyotype are molecular cytogenetic techniques, notably fluorescence in situ hybri-

dization (FISH) and array comparative genomic hybridization (Array-CGH).

Keywords

Diagnosis, Reasons for Prescription, Karyotype, Chromosomal Abnormalities

1. Introduction

The karyotype is the representation of all the chromosomes constituting the genetic heritage of an individual, the analysis of which aims to look for chromosomal abnormalities of number and structure [1]. These abnormalities have a birth prevalence rate of 43.8/10.000 in Europe [2].

The reasons for prescribing the karyotype (or clinical signs) are abnormal phenotypes which are expressed at the level of the organism by physiological dysfunctions such as reproductive disorders, mental retardation or morphological anomalies, namely congenital malformations [1].

It was discovered in 1958, the link between a clinical syndrome with mental retardation and a chromosomal abnormality (trisomy 21) [3].

Although techniques of cytogenetics have made it possible to relate phenotypic manifestations to chromosomal abnormalities, due to the variable expressivity of genetic disease, it is not easy to assess a prognosis. Indeed, Di George syndrome or 22q11.2 microdeletion (1/4000 births) is another example of a syndrome with high inter and even intrafamilial phenotypic variability despite the almost constant size of the microdeletion responsible for the syndrome [4].

In the same order, the so-called balanced diseases, in which all the genes are present, but abnormally arranged such as reciprocal translocations, are not often accompanied by morphological abnormality in carriers but can be the cause of reproductive disorders [5].

The objective of this work is to seek a possible correspondence between the reasons for prescription and the results of the karyotype in patients referred for chromosomal exploration to the laboratory of Histology-Embryology-Cytogenetics of the University Hospital of Cocody-Abidjan.

2. Material and Methods

During the retrospective study from January 2014 to December 2019 carried out in the Histology-Embryology-Cytogenetics laboratory of the University Hospital of Cocody-Abidjan (Republic of Côte d'Ivoire), 58 patient files were identified (bulletins, reports) which included the indication or reason for prescribing a constitutional karyotype and the biological result obtained (normal karyotypes, abnormal karyotypes with anomalies number and structure). Files that did not include the reason for prescribing the karyotype were not retained. The karyotypes were performed abroad.

The anonymity and confidentiality of the results were respected.

The data collected on an individual technical sheet were presented in the form of averages and percentages using Excel 2010.

3. Results

The patients were grouped according to the reason for prescribing the karyotype.17 reasons for prescription of karyotype have been identified. Sexual ambiguity was the most common reason 17 (29.3%). Of 58 patients referred for chromosomal exploration, 45 (77.6%) patients had normal karyotypes and 13 (22.4%) cases had abnormal karyotypes.

3.1. Reasons for Prescription Presenting Normal Karyotype Results

Group 1 (G1): reasons for prescription for which the karyotype result was normal, they were 10 and represented 58.82% of the reasons for prescription (Table 1).

3.2. Reasons for Prescribing the Karyotype Corresponding to a Normal or Abnormal Karyotype Then Associated Chromosomal Abnormalities

Group 2 (G2): motives whose karyotype results were normal or abnormal. Several abnormalities have been listed according to these reasons (Table 2).

4. Discussion

In this work, it comes to establishing the correspondence between alteration of the phenotype and the results of the karyotype with the help of several clinical cases. Two groups of reasons for prescription have been identified.

Group 1 (G1) represented reasons that had given normal karyotype results (Table 1). In these cases, the diagnosis of suspected chromosomal abnormalities of the referred patients was not confirmed.

Several reasons could explain these results, among which are the limits of the classic karyotype and the non-genetic causes that can induce these abnormal phenotypes (or prescription reasons).

Indeed, the karyotypes analyzed in this study were classic or constitutional karyotypes whose cytogenetic analysis has different constraints. It is impossible to access chromosomal rearrangements of small sizes inferior to 5 megabases (Mb) [6] [7].

Besides that, there are non-genetic factors that can induce abnormal phenotypes such as environmental (ionizing radiation, tobacco smoke and chemical production plants), endocrinological and anatomical factors [8]. In addition, advanced maternal age at conception (over 35 years) is associated with a type of congenital malformation [9] [10] [11] [12].

Group 2 (G2) corresponded to reasons with normal or abnormal karyotype results. Associated chromosomal abnormalities were trisomy 21, inversions and mosaics which made up of number and structure anomalies. Trisomy 21 or Down syndrome that is the dominant anomaly was found in several indications,

Table 1. Reasons for prescription presenting normal karyotype results (G1).

Motives	Results of karyotypes	Number of karyotype cases
Sexual ambiguity Cardiac pathology Early neonatal death Repeated spontaneous Miscarriage Hypogonadism Congenital adrenal gland hypertrophy Primary amenorrhea Gynecomastia Repeating clear egg Leukemia	46, XX: normal female 46, XY: normal male	29

Table 2. Reasons for prescribing the karyotype corresponding to a normal or abnormal karyotype (G2).

Motives	Karyotype results	Number of karyotype cases
Hypospadias	Normal	6
	Abnormal Mosaic: 46 X del (Y) (p11.2q11.23) [45.5%]/45, X [54.5%]	1
Deformities	Normal	6
	Abnormal Inversion: 46, XX, inv (9) Mosaic: 45, XY, −10 [7%]/46, XY, r(10) (p15.3q26.3) [93%] Trisomy: 47, XY, +21	3
Neurological disorders	Normal	2
	Abnormal Trisomy: 47, XY, +21	1
Neurological disorders and malformations	Normal	0
	Abnormal Trisomy: 47, XY, +21	1
Pubertal delay	Normal	1
	Abnormal Inversion: 46, XY, inv (9)	1
Suspicion of trisomy	Normal	1
	Abnormal Trisomy: 47, XY, +21	5
Suspicion of trisomy and cardiac pathology	Normal	0
	Abnormal Trisomy: 47, XY, +21	1
Total		29

and these are malformations, neurological disorders, suspected trisomy and cardiac pathology.

There is phenotype variability for all chromosomal abnormalities [13]. Several authors have emphasized that the phenotypic variability of Down's syndrome concerns many clinical signs of the disease, namely the importance of intellectual retardation, the inconstant presence of cardiopathy, or of a single transverse palmar crease, very early in the course of the development [14] [15].

To explain this variability and the fact that some of the phenotypic traits of trisomy 21 exist in the general population (the unique transverse palmar crease for example) or in other trisomies, hypotheses have been reported. According to Rachidi [16], it's possible that a single gene cannot cause all of the phenotypic characteristics associated with trisomy 21, rather it is more evident that many other developmental genes located on other chromosomes have a role to play in this phenomenon [17].

Other authors [18] [19] identified 3 groups of genes. Those always overexpressed, are probably involved in the constant phenotypic traits of Down syndrome like mental retardation, hypotonia or early Alzheimer's. Then, the genes with a variable level of expression could be responsible for the phenotypic variability of patients with Down syndrome, and those whose expression is identical in patients with Down syndrome and healthy patients.

The above data show the complexity of the genetic mechanisms that can be at the origin of a phenotype and its variability.

Nowadays, the resolution in cytogenetics has reached the level of the gene, making it possible to refine the genotype/phenotype correlations and therefore to improve the genetic counseling of chromosomal diseases [19].

Thus, the practitioner will have to prescribe for G1 and G2, complementary examinations to the constitutional karyotype. These are the molecular techniques of cytogenetics including fluorescence in situ hybridization (FISH) and array comparative genomic hybridization (Array-CGH). Using these molecular techniques [20], it is thus possible to highlight chromosomal rearrangements of size less than 5 Mb, unnoticed on the karyotype.

This work shows the interest of the karyotype and the contribution of various molecular cytogenetic techniques for the diagnosis of chromosomal abnormalities. Indeed, of the total of 58 patients suspected of having chromosomal aberrations and sent to the laboratory, only 22.4% had a chromosomal abnormality.

Apart from chromosomal abnormalities, these clinical signs may be caused by non-genetic factors.

5. Conclusions

The reasons for prescribing the karyotype are clinical references which may be due to environmental, endocrinological, anatomical factors, and related to maternal age alongside genetic causes.

The karyotype is a first-line examination to look for number or structure abnormalities. But in case of a phenotype suggestive of chromosomal anomalies

and the absence of abnormal karyotypes in patients referred, it is necessary to resort to other high-resolution cytogenetic techniques, in particular fluorescence in situ hybridization (FISH) and Array comparative genomic hybridization (Array-CGH).

Authors' Contributions

ZPD and MJAD contributed to acquisition of results and their interpretation. QDC, MOAB, BYEB, AJLO, BD, MIJMD and GVY revised critically for important intellectual content.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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