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Abstract

Microarray-based comparative genomic hybridization (aCGH) is commonly used in diagnosing patients with intellectual disability (ID) with or without congenital malformation. Since aCGH interrogates the whole genome, there is a risk of being confronted with incidental findings (IF). In order to anticipate the ethical issues of IF with the generalization of new genome-wide analysis technologies, we questioned French clinicians and cytogeneticists about the situations they have faced regarding IF from aCGH. Sixty-five IF were reported. Forty corresponded to autosomal dominant diseases with incomplete penetrance, 7 to autosomal dominant diseases with complete penetrance, 14 to X-linked diseases, and 4 were heterozygotes for autosomal recessive diseases with a high prevalence of heterozygotes in the population. Therapeutic/preventive measures or genetic counselling could be argued for all cases except 4. These 4 IF were intentionally not returned to the patients. Clinicians reported difficulties in returning the results in 29% of the cases, mainly when the question of IF had not been anticipated. Indeed, at the time of the investigation, only 48% of the clinicians used consents mentioning the risk of IF. With the emergence of new technologies, there is a need to report such national experiences; they show the importance of pre-test information on IF.

Key Word : aCGH, ethical issues, incidental findings, pre-test information

Introduction

An incidental finding (IF) is defined as a non-deliberate finding that has potential health or reproductive importance for the proband or his family and is not related to the indication of the test. IF are not uncommon in clinical practice and recommendations about their report have been established. It is widely accepted that an IF should be returned when it reveals a condition likely to be life-threatening, a condition likely to be severe that can be avoided or improved, or genetic information that can be used in reproductive decision-making[1].

Microarray-based comparative genomic hybridization (aCGH) has become a first-intention diagnostic tool in intellectual disability (ID)/developmental delay (DD), dysmorphism, multiple congenital abnormalities (MCA), associated or not with behavioural disorders, seizures or aberrant growth patterns, as it allows an objective interrogation of chromosome structure for microscopic and submicroscopic imbalances throughout the genome. Human genomes exhibit substantial variation; the average diploid human genome differs from the reference genome by ~3 million to 3.5 million single-nucleotide variants (SNP) and about a thousand copy-number variants (CNVs; e.g., DNA deletions and duplications) >500 base pairs in size[2]. Most CNV do not have any clinical implication but some are found in human diseases, or have unknown significance. In the search for a CNV that causes a patient's phenotype, there is a risk of being confronted with IF since aCGH is a pangenomic test. When aCGH reveals a diagnosis in a patient, the IF can be located either outside or within the rearrangement. In other cases, an IF could be found, but the cause of the phenotype may remain unknown. Ethical issues of IF after the prescription of aCGH have been studied by some groups[3,4,5,6,7] , but the experience of clinicians in the transmission of the results to patients and/or their families is still insufficient.

With the arrival of new technologies such as Next Generation Sequencing (NGS) for

diagnostic purposes, allowing whole exome or genome sequencing, the management of IF will become a crucial ethical issue for medical geneticists and biologists, since they are expected to become more frequent. The American College of Medical Genetics and Genomics (ACMG) recently published a policy statement, which recommended that laboratories performing clinical sequencing seek and report pathogenic or probably pathogenic mutations in a list of 56 genes of medical value for patient care[5, 8]. These recommendations have been subject to intense discussion/controversy, thus showing the need to accumulate experience and advice, which might vary from one country to another (www.acmgfoundation.org). In particular, they emphasized the importance of disclosing the possibility of such results in pre-test discussions with patients.

In order to take advantage of the experience of IF found by aCGH, we analysed the management of IF revealed by this technique in France over a 7-year period.

Materiel and Methods

The methodology was designed to question clinicians about their experience in returning IF during the first 7 years of their experience with aCGH. Since the design of the study was retrospective, various types of array were used, from BAC array to SNP array with a resolution of 300K. Coverage generally increased over the 7- year study period. Nevertheless, Agilent 180K was the most commonly used array (30% of the laboratories). For the purpose of the study, we used the following definition of IF: the finding of pathogenic or probably pathogenic alterations in genes that are not apparently relevant to the diagnostic indication for which the test was ordered, but that have potential health or reproductive importance for the proband or his family. It differed from the ACMG recommendations since the search was not deliberate, but incidental[8].

Two different questionnaires (supplemental data 1 to 4) were produced, sent out in January 2014, and collected at the end of March 2014. The questionnaires had been validated beforehand by a group of medical geneticists, cytogeneticists, molecular biologists and ethicists. The first questionnaire was sent to all the French clinical geneticists who were members of the « Association Française des Généticiens Cliniciens » and involved in genetic clinics and in prenatal diagnosis (PND) on a daily basis. Besides administrative data (sex, age, center), the first part of the questionnaire included general questions such as the number of aCGH prescribed each year, the number of IF they had been confronted with, and the mention of the risk of IF in the informed consent. The second part of the questionnaire included one sheet for each IF. Clinicians were asked to give the sex and age range of the patient concerned, the coordinates of the CNV, the type of CNV (deletion or duplication), and its inheritance (inherited, de novo or unknown). For IF that may be responsible for an autosomal dominant disease, they were asked to say whether the penetrance of the disease was complete or incomplete, and provide the category of IF (genetic predisposition to cancer, to neurogenetic diseases, to cardiogenetic diseases, or to other categories of disease). In cases of heterozygosity for an autosomal recessive disease, the clinician was asked to provide the information only for frequent diseases that would usually indicate carrier testing in the proband's family, according to the carrier frequency in the ethnicity concerned (cystic fibrosis and spinal muscular atrophy in Caucasians, for example), or rare variants in a consanguineous family. The clinician was then asked to say whether the IF was returned to the patient and/or general practitioner in charge of the patient, whether he/she had encountered any difficulties during the interview while returning the IF, and whether a psychological interview was proposed to the patient/family. The answers were correlated with the characteristics of the disease, i.e. if it was accessible to therapeutic or preventive measures, genetic counseling and/or prenatal diagnosis. The clinicians were

finally asked whether the decision to return the CNV was discussed in a multidisciplinary meeting (with other clinicians and biologists within the same genetics department) or not. The French cytogeneticists from the national Achropuce network were also asked to fill in a questionnaire in order to maximize the number of reported case. They were asked to give, the coordinates of the CNV, the type of CNV (deletion or duplication) and its inheritance (inherited, de novo or unknown), and to indicate if they returned the IF to the clinician. If a clinician did not declare an IF to the study reported by a cytogeneticist, he/she was then contacted.

The pathogenicity of each IF declared was determined using the information available from public databases including OMIM (http://www.omim.org/), UCSC (https://genome.ucsc.edu/), Decipher (https://decipher.sanger.ac.uk/), Clingen (http://clinicalgenome.org/), Pubmed (http://www.ncbi.nlm.nih.gov/pubmed) and Standard For Cytogenomic Array (ISCA) consortium (http://dbsearch.clinicalgenome.org/). We classified an IF as pathogenic if it had already been reported in the literature as causing the disease; probably pathogenic if the IF comprised a gene in which mutations are known to cause the disease secondary to haploinsufficiency; of unknown significance in the remaining cases. In this study, we did not include susceptibility factors for disease.

Results

We collected data from all university hospitals in France and from 55% of the

practitioners. Sixty-five IF (table and supplemental data 5) that corresponded to our definition were reported by 44 clinicians. 7 IF declared were rejected because they did not fit our criteria, they consisted in heterozygous status for recessive autosomal disease with very few heterozygotes in the general population. All the aCGH were prescribed for developmental delay, intellectual disabilities and/or malformations. The majority of IF were found in children. Eight were detected in adults and one in a fetus, after termination of the pregnancy. Three were diagnosed antenatally (none leading to termination of the pregnancy).

Among these 65 IF, 40 corresponded to autosomal dominant (AD) disease with incomplete penetrance (including 19 predispositions to cancer), 7 to AD disease with complete penetrance, and 14 to X-linked disease (2 in male and 12 in female carriers) (Table 1). Three heterozygotes for prevalent autosomal recessive (AR) disease were reported and one heterozygote for a rare disease in a highly consanguineous family. Therapeutic/preventive measures (including prenatal testing) could be argued for all cases except 4. Among the 65 IF, 55 (85%) were returned to the patients, but only 4/65 (6%) were intentionally not returned (Supplemental table). Indeed, for 5 patients, the consultation was either planned at the time of writing, or the family did not come to their appointment. The 4 results that were intentionally not returned to the patient/family included one paternally inherited deletion of *TTBK2* that could be responsible for the development of spinocerebellar ataxia type 11 (OMIM #604432) in a negative family history, one *de novo SETX* deletion that could be responsible for the development of juvenile amyotrophic lateral sclerosis type 4 (OMIM #602433), one *de novo* duplication of *PARK4* that could be responsible for the development of Parkinson disease (OMIM #605543) and a *PMP22* deletion that could be responsible for the development of Hereditary Neuropathy with liability to Pressure Palsies. For the 3 first cases, and after discussion in a multidisciplinary meeting, the results were not returned because of the

uncertain significance of the rearrangements, the late onset of the symptoms, and the absence of treatment or preventive measures. In the fourth case, the result was not returned because the adult patient had not been informed of the possibility of incidental findings before the test. Seven of the 65 IF were due to the deletion/duplication of a gene included within the pathogenic CNV. In one case, a *PKD2* deletion responsible for polycystic kidney disease (OMIM #173900) was already known in the family of the patient but this patient had not been diagnosed, which led us to consider this result an IF.

When clinicians returned the results, they reported difficulties in 19 cases (29%). In 9/65 cases (14%), the clinician said that it was difficult to give an accurate prognosis to the patient/family, in cases of *DMD* deletion (causing Duchenne Muscular Dystrophy, OMIM), *TP53* deletion (causing Li-Fraumeni syndrome, OMIM #151623), *PMP22* duplication (causing Charcot-Marie-Tooth syndrome 1A, OMIM #118220), in the absence of symptomatic family members. In 6/65 cases (9%), the family did not understand the results (one carrier status for Duchenne Muscular Dystrophy, one carrier status for Farber disease (OMIM #228000) and four cases of *PMP22* deletion). In 4/65 cases (6%), the parents found it difficult to cope with the announcement, in the context of a genetic predisposition to cancer. In 3 cases, the results were unexpected and caused parental anxiety. In 1 case, the parents were surprised of receiving additional information 5 years after the result of the pathological CNV since the IF was inside the pathogenic deletion. Indeed, the clinician asked the laboratory for the gene content on the occasion of a follow-up visit; information that was not given at the time of the first results. Among the 44 clinicians who took part in our study, 30 (68%) thought that consent should leave the choice to the patient to know his/her status for an IF, and only 21 used a consent form that mentioned the risk of IF (48%) at the time of the analysis in a given patient.

Discussion

IF are not uncommon in the medical domain and general recommendations about their report have been proposed. IF should be reported when there is a strong net benefit for the patient or his/her offspring to know the information[1]. The report of IF in the context of genetic characteristics raises additional questions since the results may have no impact on the health or reproduction for the patient him/herself, but may be important for his/her family. Therefore, specific studies are needed in order to develop specific recommendations. Few studies about the experience of physicians in the management of IF following the prescription of aCGH in routine clinical practice have been published [9,10,11], thus justifying the present study.

The aim of this study was to analyze 7 years of experience regarding IF after the prescription of aCGH in France. The methodology used did not permit us to determine a reliable frequency of IF arising from aCGH since it did not involve a systematic bioinformatics search on standardized criteria, and only relied on the physician's report, which could be subject to recall bias given the time frame of the surveyed. The majority of results concerned AD diseases with incomplete penetrance, inherited or not from an asymptomatic parent. When X-linked inheritance was concerned, it was found more frequent in females, with no immediate consequences for the patient, but with consequences for reproductive issues of the patient and relatives. Similarly, we found only 4 carrier status for a recessive disease according to our definition, which had no immediate consequence for the patient but was an indication for genetic counseling for the family and for future pregnancies. Seven of the 65 IF were included within the pathogenic microdeletion/duplication, and the incidental character could be regarded as debatable since in some cases they may be considered part of the patient's phenotype. Only four IF were detected prenatally. This may be due to the use of lower resolution array by some laboratories in order to avoid IF, but also because the prenatal use of aCGH is quite recent in France and not available in all centers.

In our study, geneticists did not return the results in only 4 of the 65 cases. All of the geneticists gave the IF result to their patients when there was strong evidence of a benefit, such as treatment, particular care or genetic counseling to avoid complications. The only incidental results that were not returned to the family were those concerning adult-onset diseases with no preventive care and no available therapy, but also insufficient data for their pathogenicity, and the decision was made after a collegial discussion. Returning an IF may cause difficulties for clinicians because the consequences can be uncertain. This point has been learned from the experience with DMD duplications/deletions[12,13,14] , not all *DMD* rearrangements are pathogenic[9,15,16,17,18,19], thus underlining the importance of familial screening. Indeed, in our study, we found 11 cases of rearrangements comprising DMD. In 2 cases, the familial segregation argued in favor of a polymorphism, but returning the result caused anxiety in the family in the absence of formal conclusions. These data should lead to caution in returning the results to families, and a rearrangement should be considered pathogenic only when it has already been reported to be related to the disease in previous publications or databases. In our study, only 79% of the IF could be considered pathogenic or probably pathogenic. The significance was unknown in 21% of IF, thus making it difficult for the clinician to give an accurate prognosis and for the patient to understand the significance and to cope with the finding.

Some authors suggest that the majority of patients would like to know about these results in order to cope and to make future reproductive decisions. These findings were based on telephone interviews with the parents of children affected by a rare disease,[21,22] but opinions are mixed in other studies[3,4]. In a study conducted by Kleiderman[3] concerning the discovery of IF in whole exome sequencing (WES) investigations, responders expressed an overwhelming interest in receiving the child's sequencing results but were less confident that they would want to know the results if the disorder was a highly penetrant and fatal adult-onset illness. For the carrier status for a recessive condition, they

expressed the wish to be informed later, when the information became relevant for their child[3]. These results were confirmed in a study conducted by Christenhusz[4], who emphasized the fact that parental motivations for and against the disclosure of unexpected results clustered around four main themes: actionability; knowledge about the future of their child; context (relationship with geneticist, disabled child); and characteristics of the result.

Following these studies, it appears essential to know the wishes of each patient/family. However, it seems that this was not anticipated in each case since only 48% of the centers in our study used consent form mentioning the risk of IF at the time of the analysis in a given patient. Most of the geneticists answered that the consent should give the patient the choice of whether to know the IF or not. Nevertheless, we learned from the literature that patients and their families admitted they could not anticipate their own preferences about whether or not to receive results until they were returned, given the variability of the potential results and their implication[3]. Another ethical debate was raised by the ACMG, since they published recommendations in order to systematically search for pathogenic mutations in 56 genes implicated in cancer predisposition or in cardiovascular diseases[7,8,21]. In the case of systematic screening for a particular gene, the term IF cannot be used and some authors prefer the term secondary findings. The arrival of new technologies raises questions about current practices in presymptomatic testing. Indeed, in France, presymptomatic testing in children for adult-onset diseases is not allowed, and requires special testing conditions for adults, including a psychological interview.

The largest study about IF in aCGH identified IF in almost 1% of aCGH performed in a routine clinical population [9]. However, using exon-targeted aCGH only 40% of these IF were found to be pathogenic or probably pathogenic. Indeed, Boone et al used custom-designed targeting for 24,000 exons of 1,700 clinically relevant and candidate disease-related genes in addition to usual probes of the Agilent 180k microarray in unscreened or

undiagnosed individuals and their parents when available that may reveal a higher proportion of intragenic exonic IF[15]. They discovered 83 IF in a cohort of 9,005 DNA samples. They used a different definition since they regarded as an IF only late-onset disorders unrelated to the current diagnosis of the patient.

In conclusion, this study reflects the difficulties encountered by clinicians in routine practice and the way they have managed them. Accurate pre-test counseling seems essential when prescribing this kind of pangenomic test. More studies are needed to evaluate the preferences of patients in the management of their IF.

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Table: Repartition of the 65 IF.

		AN	<5y	5-18y	>18y	Total
Inheritance						
Dominant autosomal	Complete penetrance	0	4	3	0	7
	Incomplete penetrance	2	15	19	4	40
Recessive autosomal (heterozygote status)		1	2	1	0	4
X-linked	Male	0	2	0	0	2
	Female	0	6	5	1	12
Disease						
Cancer predisposition		0	13	9	0	22
Neurological disease		1	6	11	4	20
Sudden death predisposition		1	0	1	0	2
Carrier status		1	8	6	1	16
Other		0	2	3	0	5

AN: Antenatal