Incidental Finding in Copy Number Variation (CNV) Analysis

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Abstract When interrogating the human genome, the most significant finding at times might not even be the one related to the referring diagnosis. Such incidental findings (IFs) can pose challenges with regard to which results should be revealed? Such issues have begun to be addressed with the recent American College of Medical Genetics and Genomics (ACMG) recommendations for reporting IFs in clinical exome and genome sequencing; however, copy number variants (CNV) were not specifically addressed. The recommendations found that while some incidental CNV findings are currently of uncertain clinical significance, others are medically actionable. The reporting of the incidental CNVs can have a significant impact on risk counseling for future pregnancies and other family members at risk as well as enabling interventions to improve health outcomes. According to the ACMG recommendations, in the course of performing chromosomal microarray analysis in 3,500 “normal” parental samples for interpretation of variants of unknown clinical significance in the proband, we incidentally found 28 (0.8 %) clinically relevant CNVs that were reported back to the physician to be communicated to the patient. Reporting of IFs is not new to medicine, so should reporting IF in whole genome analysis be any different? Should the current ACMG recommendations for reporting IFs be updated to incorporate incidental CNVs?

Keywords Chromosomal microarray analysis · Incidental finding · Copy number variation

Introduction

Incidental findings (IFs) are defined as clinical or research findings that are unrelated to the primary indication but may have potential health or reproductive importance [1]. IFs are intrinsic to medical practice and the most frequently published IFs are in the context of medical imaging. For example, neoplastic and non-neoplastic IFs on brain MRI are common with a prevalence of 0.7 and 2.0 %, respectively, that increases with age [2]. Furthermore, computed tomographic colonography (CTC), a promising alternative to traditional colonoscopy, allows evaluation not only of the colon, but also visualization of the lung bases, the abdomen, and the pelvis. This imaging technique reports a high incidence (33–895 %) of IFs, of which the majority is of low or medium clinical importance [3]. In genetic studies, the earliest examples of IFs are the misattribution of paternity identified in the course of establishing family pedigrees with an estimated incidence of 10 %, though this figure is poorly supported and more studies are needed [4].

The past decade has seen an explosion in our understanding of the role of genetics in human disease through the introduction of whole genome scan-analyses, such as Chromosome Microarray Analysis (CMA), whole genome, and whole exome sequencing (WGS, WES). With the adoption of these new technologies, new legal, ethical, and psychological implications have risen. One pressing ethical challenge is the reporting of IFs [5–8]. Should all IFs be reported back to the patient, or only the clinically actionable ones? [9–11]. While reporting of IFs in the pediatric population, maintaining pediatric autonomy also needs to be considered

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Fig. 1 Array profile on a parent showing the same two CNVs as in the child in addition to a deletion in 17p12 involving *PMP22*. Deletions of *PMP22* are associated with Hereditary NEUROPATHY with liability to pressure palsy (HNPP)

[12]. With the dynamic nature of knowledge, any effort to develop a consensus list of IFs to be reported becomes outdated rapidly and therefore patient education, informed consent, and genetic counseling will have to be an integral part of all genome-wide level genetic testing [13–15].

Introduction of CMA, a high resolution copy number genomic analysis, to clinic practice in the last decade has led to the identification of many new microdeletion and microduplication syndromes and also variants of uncertain clinical significance (VUS) [16, 17]. Presently, there are approximately 211 microdeletion syndromes and 79 microduplication syndromes reported in the literature [18]. Although CMA has been in clinical practice longer than next-generation sequencing technologies (WGS, WES), the contribution of CNVs to the incident alone remains under explored. There are only a few reports addressing IFs involving CNVs in patients, as summarized below. Our group [19] reported IFs of CNVs in a cohort of 9,005 pediatric individuals, in which 83 single gene CNVs affecting 44 unique genes associated with adult onset disorders unrelated to the referring indication were identified. Fourteen of these CNVs were classified as most likely disease causing, 25 were benign, and 44 were of unknown significance. There have also been a couple of studies looking at cancer disposition IFs by CMA [20, 21]. Pichert et al. [20] in their patient population of 4,805 found 29 (0.6 %) patients had a CNV of <5 Mb that contained a cancer predisposition gene. Only 6 of these patients were referred for a syndrome involving the cancer predisposing gene, while 23 patients had no symptoms or family history of a cancer syndrome. Four of these CNVs were inherited, eight were de novo, and the inheritance in the rest could not be established. Adams et al. [21] identified 34 ($34/18,437 = 0.18$ %) individuals with a CNV encompassing a cancer predisposition gene. Ten of these patients had an indication of a cancer predisposition syndrome; however, 24 patients had a non-specific indication. Furthermore, 27 of 34 patients were under the age of 5 at the time of CMA.

Interpretation of CNVs of unknown clinical significance (VUS) is difficult in the postnatal setting and even more so in a prenatal setting. Parental CMA to determine if the VUS is inherited or de novo is usually the first line of testing. If the VUS is inherited, and the parent has a “normal” phenotype, it is interpreted as most likely benign, while if de novo the clinical significance is left as unknown. It has been recently discovered that submicroscopic CNVs are as important as SNPs, short tandem repeats (STRs) and other small changes in their contribution to genome variation. These structural variations could be large and may or may not contain genes, regulatory regions, and non-coding regions. Although many of these have no phenotypic consequence, some may affect gene dosage and could be implicated to cause disease as mentioned earlier. It is theorized that an average individual may have up to 100 CNVs >50 kb in size [22]. Therefore, a parental CMA study to determine the inheritance status of a CNV present in their child can potentially uncover a clinically significant IF.

There have been no reports of the incidence of identifying a clinically significant CNV IF in a cohort of “normal” parental studies. In the course of performing chromosomal microarray analysis (CMA) in 3,500 “normal” parental samples in our institution for interpretation of variants of unknown clinical significance in the proband, we incidentally found 28 (0.8 %) clinically relevant CNVs including mosaic or full chromosome aneuploidies, genomic disorders with incomplete penetrance, carriers of X-linked Mendelian traits, carriers of autosomal recessive disorders, cancer susceptibility, and dominant adult onset disorders. None of these IFs were seen in these parents’ children.

The whole chromosome aneuploidies included a mosaic trisomy 3, which has not been reported in a constitutional case; however, it could be an acquired change as in non-Hodgkin’s lymphoma, though the father was lost to follow-up. Two others cases involved maternal samples with trisomy X and mosaic monosomy X (10 %). There were 8 cases where a CNV was observed in a genomic region that

is associated with a variable phenotype, such as a duplication in 1q21.1, duplication of 16p13.11, deletions and duplications of the *CHRNA7* gene, duplication in 22q11.2, and also a duplication of 6 Mb of the Prader Willi region (15q11.2q13) was observed in one mother. Three females were found to be carriers of an X-linked disorder (deletions in the *DMD*, *F8* and *CHM* genes). One parent was found to be a carrier of two autosomal recessive CNVs, one in the *NPHP1* and one in the *GLDC* gene. Deletion and duplication CNVs in the *PMP22* gene associated with Hereditary neuropathy with liability to pressure palsy (HNPP) and Charcot Marie Tooth type 1A (CMT1A) were identified in 3 individuals. CNVs encompassing cancer disposition genes were observed in 2 individuals: a 3.9 Mb duplication involving the *N-MYC* gene and a deletion in the *PMS2* gene. All of these IFs were reported back to the parent and follow-up with the appropriate clinicians was recommended. Figure 1 shows a CMA profile on a parent that was identified to carry a deletion of the *PMP22* gene associated with HNPP.

As genomic technologies continue to advance and cover the entire genome, the IF problem will grow. We are currently in the early stages of development in determining how to handle IFs. Systematic research into the prevalence, different types of IFs (CNVs vs sequence-level mutations), the cost of evaluation of these IFs (positive or false positive), and clinical follow-up is needed to determine the best approach of dealing with IFs. Currently there is growing consensus among genetic professionals of reporting back of actionable IFs, but there is less support of reporting non-actionable IFs. Ultimately, views of the genetic professionals and the lay public will be instrumental in defining policies for disclosure of IFs from whole genome analysis.

Disclosure A Patel and W Bi both declare no conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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