BROAD MULTI-GENE PANEL OR WHOLE EXOME SEQUENCING IN MALFORMED FETUSES REVEALS EIGHT DEFINITIVE AND ONE LIKELY DIAGNOSES IN FIFTEEN STUDIED FETUS, IN PRENATAL SETTING

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BACKGROUND

Recently, broad multi-gene panel or whole exome sequencing by Next-generation Sequencing (NGS) became available in the clinical practice at our center. Here we present the results from the first fifteen fetuses to which exome sequencing was offered in two prenatal diagnosis centers and assessed in the same laboratory.

METHODOLOGY

After diagnosis of sonographic abnormality and medical termination of pregnancy (13), or foetal death with multiple anomalies confirmed at autopsy (2), a predefined panel of 4813 genes (13) or a trio whole exome sequencing (WES) (2) were performed, following a previous extensive evaluation.

RESULTS AND DISCUSSION

A definitive diagnosis was achieved in eight cases and a likely diagnosis in one (Table 1). The very high diagnostic yield achieved likely derives from cohort ascertainment: recurrence was present at five of the nine families (Figure 1) and very severe, but viable, phenotype, in other two. After genetic diagnosis we found a high recurrence risk in six of the nine families: five with autosomal recessive (AR) diseases and one X-linked (XLR) (Figure 2) – with 25% recurrence risk for future pregnancies and 50% for male pregnancies, respectively. From these six families, four had another pregnancy after diagnosis: two of them were offered prenatal diagnosis (PND) and the other chose to resort to IVF with egg and sperm donor (Table1).

The likely diagnosis of Fanconi anemia was based on clinical findings. Though we found two potentially pathogenic variants in genes that cause Fanconi anemia disorders (FANCC and FANCD2), they are both of AR inheritance (Fanconi anemia, complementation group C [MIM 227445] and Fanconi anemia, complementation group D2 [MIM 227464], respectively). A digenic inheritance of Fanconi anemia has not been described to date, however it is known that the FANCC gene product interacts in a multiprotein complex whose main function is the post-translational activation of the FANCD2 gene (Hartmann et al., Am J Hum Genet., 2010).

In the six couples without a diagnosis, we observed recurrence in five (Figure 1). From these recurrent cases, we suspect: of non-monogenic disease in two of them [one with visceral heterotaxy, an highly recurrent disorder even if with unknown etiology; and one with polymalgiaformosus defects at all three pregnancies]; intra-uterine lethality with unknown gene in other two [one with pancreatic agenesia and one with isolated bilateral foot and neonatal death in both fetuses of a dizygotic twin pregnancy]; and an AR disease in the remaining one [in which we identified one mutation in a gene that causes an AR disease compatible with the phenotype, but failed to detect a second mutation].

At last, from the fifteen cases in study we found unsolicited findings in three (Table 1). In one of them the mutations responsible for the unsolicited finding were also the causal mutations – AR1R2 gene, causes not only Minirene myopathy (MIM 255320), compatible with the observed phenotype, but also Malignant hyperthermia susceptibility 1 (MIM 145600). In other case, we found a pathogenic inherited RARF gene mutation associated with Dilated cardiomyopathy 1N (MIM 615916), possible compatible with the mild cardiopathic signs present in the father. The mutation at MYHPC3 was described in patients with hypertrophic cardiomyopathy, evaluation of the couple is pending.

Table 1. Sample description and detailed results. The clinical indication, obstetric history and results are detailed per case only for those in which a diagnosis was achieved.

![Table 1](image)

![Figure 1](image)

![Figure 2](image)

CONCLUSION

At the moment, our proposal is to restrain the use of clinical exome or WES to cases with recurrence or high severity and only if collaboration with a medical geneticist is assured. In a short future, the use of these tests will increase and become part of the initial diagnostic approach.