Development of an NGS-based solution for the identification of individuals carrying recessive genetic mutations in reproductive medicine


1 qGenomics, R&D department, Barcelona, Spain.
2 Hospital Universitari Quirón Dexeus, Department of Obstetrics Gynecology and Reproduction, Barcelona, Spain.
3 Universitat Pompeu Fabra, Genetics Unit. Health and Experimental Sciences Department, Barcelona, Spain.

Study Motivation

- Identification of couples at risk of transmitting a recessive genetic disorder allows them to take informed and responsible actions regarding their reproductive plans.
- Next Generation Sequencing (NGS) is revolutionizing genetic research and diagnosis in reproductive medicine.

Can NGS technologies efficiently evaluate the carrier status of most commonly mutated genes in recessive disorders?

Carrier Genetic Screenings until now
- Targeted Mutation SNP-based microarrays
  - Only known mutations
  - Point and small insertions/deletions
  - Increased residual risk
  - In principle no variants of unknown significance (VOUS)

NGS Carrier Screening developed (qCarrier)
- More genes and diseases
- Any type of mutation
- Cost-effective
- Reduced residual risk
- Higher chance of VOUS detection

Study Goal

Development of an NGS-based approach targeting genes causing prevalent and severe recessive diseases for testing healthy couples undergoing ARTs and egg/sperm donors in donation programs, to reduce the odds of passing a recessive or X-linked disorder to the offspring.

qCarrier Study Design - Participants/materials, setting, methods

Sequence capture
- Selected genes causing 180 recessive disorders
- 210 genes

NGS
- High throughput sequencing of captured targets

Bioinformatics
- Identification of point mutations, indels and copy-number rearrangements

Validation Main Results

All but one (48/49) different mutations were correctly scored in the blinded study and only one deletion-type mutation remained undetected. This information allowed us to finely tune the algorithm to reach maximum sensitivity. All single nucleotide changes were validated and no known recessive mutations were called in the control samples.

First Clinical Results

Table 1. Number of subjects

| Table 2. Carrier Detection by Disease |

Table 2. Summary of mutation detection: 102 pathogenic recessive mutations detected. 66% (61/90) patients were carriers of Mendelian diseases. Mutations identified included known pathogenic alleles (F508del, Factor V Leiden, 5T poly-T).

Rare variants and new severe mutations (frameshift, nonsense, splicing) were also identified, not detectable by other screening methods.

Conclusions

- NGS increases carrier detection rates of recessive diseases.
- This test can be applied in donor/receptor matching and in a preconception context for couples willing to know genetic risks.
- Current knowledge of the real extent of human genetic variation might be a major limitation in data interpretation.

Identification of previously unknown variations challenges the communication of results. Our findings also demonstrate that previously reported disease-causing mutations are not real. This emphasizes the absolute need for an adequate pre and post-test genetic counselling that clearly states the advantages and limitations of the current knowledge.