Comprehensive Carrier Screening using a combination of NGS panel, ddPCR and RPA

Florian Vogel, Katja Brüsehafer, Shivendra Kishore, Krishna Kumar Kandaswamy, Maximilian Weiss, Gabriela-Elena Oprea, Arndt Rolfs, Peter Bauer[1]

[1] CENTOGENE AG, Rostock, Germany

Carrier screening is a genetic test used to determine if a healthy person is a carrier of a recessive genetic disease. The goal of carrier screening is to help individuals understand their risks of having a child with a genetic disorder and review the range of options available to guide pregnancy and family planning.
In order to provide a comprehensive screening panel, a set of 331 genes relevant for autosomal and X-linked recessive disorders was selected. The CentoScreen® test includes a NGS panel targeting the 331 genes (assessing CCDS +/-20 bases and relevant deep intronic mutations from HGMD® and Centogene's proprietary variant database CentoMD®) and an in-house developed pipeline provides CNV calling on NGS data. Technically challenging but relevant risk genes (FMR1, SMN1, CYP21A2) are analyzed by additional assays based on ddPCR, RPA and Sanger.

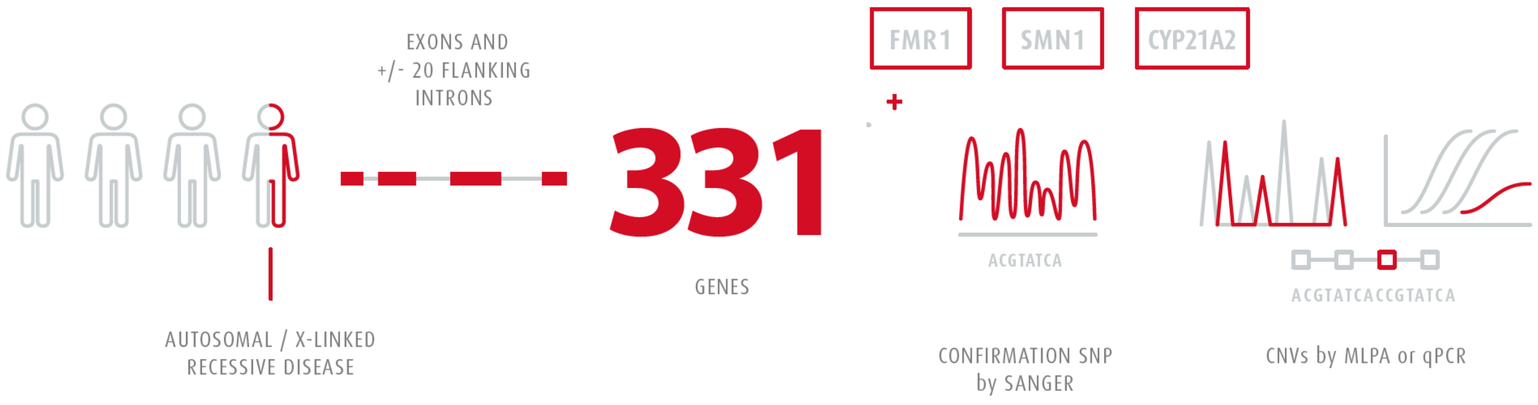
Why carrier screening is important

- An individual is a carrier of ~2.8 pathogenic variants on average[2]
- Approximately 1 in 4 (24%) individuals are carriers for at least 1 disorder and 1 in 20 (5.2%) are carriers for multiple disorders [3]
- The American College of Obstetricians and Gynecology recommends offering carrier screening to all pregnant women or couples considering pregnancy[1]

Selection of disorders and targeted genes

- Early onset and high-severity disorders
- Well-defined phenotype
- High carrier frequency
- Availability of treatment
- Severe effect on quality of life

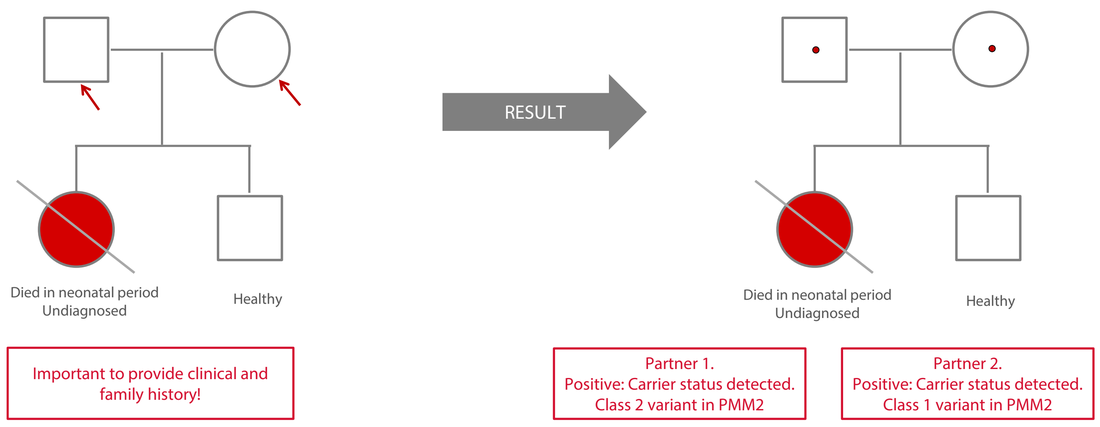
CentoScreen ®



- ≥99% of targeted genes covered at ≥ 20x by NGS for 331 genes
- Additional analyses for FMR1, SMN1 and CYP21A2
- Confirmation of low quality SNPs by Sanger, all CNVs by qPCR or MLPA

Case I: Family history and preconceptional testing

- Previous undiagnosed deceased child
- Child had no genetic testing
- Suspected diagnosis of CDG1a
- Couple worried about recurrence risk and other disorders



Important to provide clinical and family history!

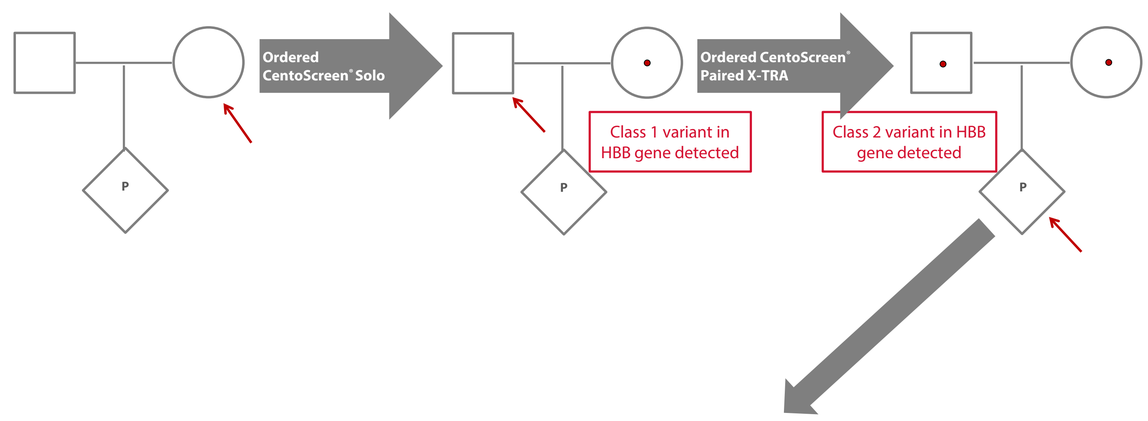
Partner 1.
Positive: Carrier status detected.
Class 2 variant in PMM2

Partner 2.
Positive: Carrier status detected.
Class 1 variant in PMM2

Available options for family planning:

- Prenatal diagnosis in CVS or AF sample possible
- Pre-implantation genetic diagnosis possible
- Using a sperm or egg donor
- Carrier testing for other family members at risk

Case II: No family history



Prenatal testing for fetus is now possible and available at CENTOGENE for Thalassemia

References

1.Committee Opinion No. 690. American College of Obstetricians and Gynecologists. (2017) Obstet Gynecol.129:e35–40
2.Bell CJ, et al. (2011) Sci Transl Med.3(65):65ra4
3.Lazarin et al. (2013) Genet Med.15(3):178-86

Disclosure of conflict of interest:

Data presented here was sustained in part by CENTOGENE AG, Rostock,; Author of the presentation, Florian Vogel, and all co-authors are employees of Centogene AG, Rostock, Germany

CENTOGENE
THE RARE DISEASE COMPANY

www.centogene.com

CLIA #99D2049715

CAP ACCREDITED COLLEGE of AMERICAN PATHOLOGISTS

ISO 15189 CAP ACCREDITED COLLEGE of AMERICAN PATHOLOGISTS