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Identification of candidate breast cancer predisposing genes by sequencing extended panel of 492 cancer associated genes in BRCA1/2 negative probands

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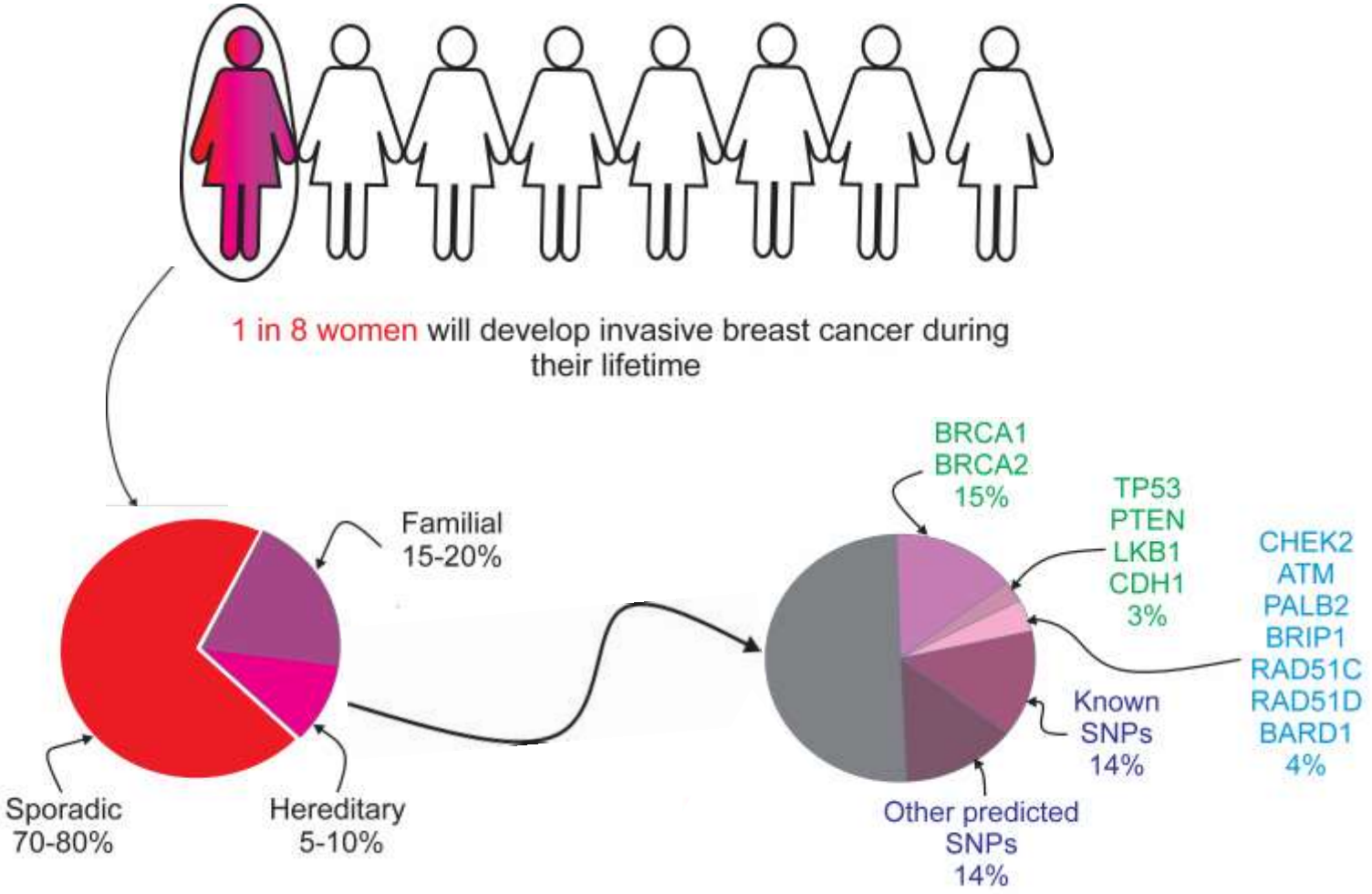
Introduction



What are those ***missing breast cancer predisposing genes?***

Couch FJ et al.,Science 2014;343(1466)

Research Rationale

Hereditary Breast Cancer Genes → Other Cancers/Cancer Syndromes

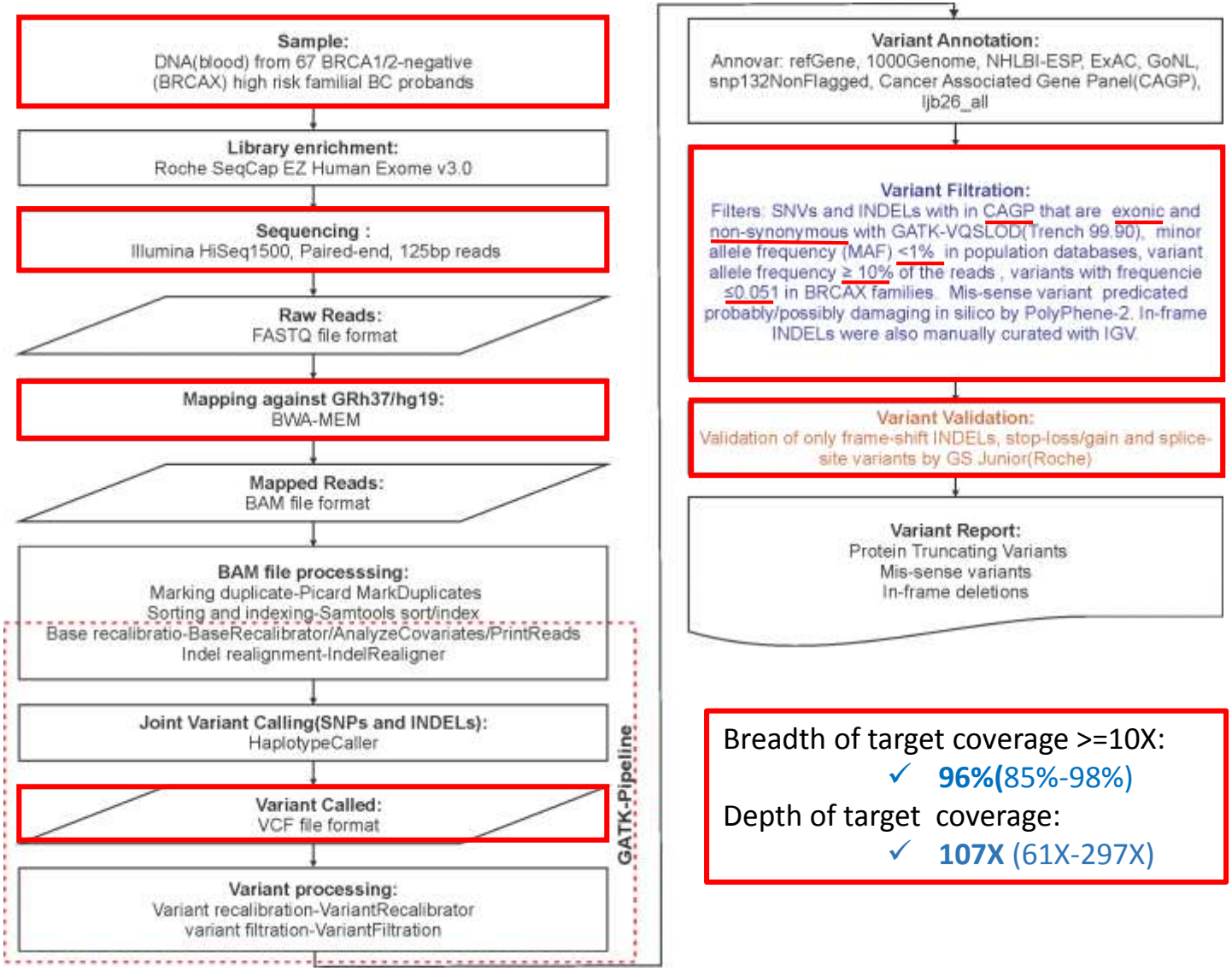
BRCA1 & BRCA2	Ovarian cancer
	Prostate cancer
	Pancreatic cancer
	Melanoma cancer
TP53	Li-Fraumeni syndrome
PALB2	Pancreatic cancer
CHEK2	Colorectal cancer
CDH1	Hereditary diffuse gastric cancer (HDGC)
PIK3CA & AKT1	Cowden and Cowden-like syndromes
RINT1	Lynch syndrome
NF1	Neurofibromatosis 1

Hereditary Breast Cancer ← Other Cancers/Cancer Syndromes Genes

492 Cancer Associated Gene Panel (CAGP) → 67 BRCAX (probands) ⇢ Other Family Members

Mai, P.L., *et al.* PLoS One 4, (2009); Jones, S., *et al.* Science 324, 217 (2009) ; Norton, J.A., *et al.* Ann Surg 245, 873-879 (2007); Orloff, M.S., *et al.* Am J Hum Genet 92, 76-80 (2013); Park, D.J., *et al.* Cancer Discov 4, 804-815 (2014); Friedman, J.M. GeneReviews(R) (eds. Pagon, R.A., et al.) (Seattle (WA), 1993).

Sequencing and data analysis workflow



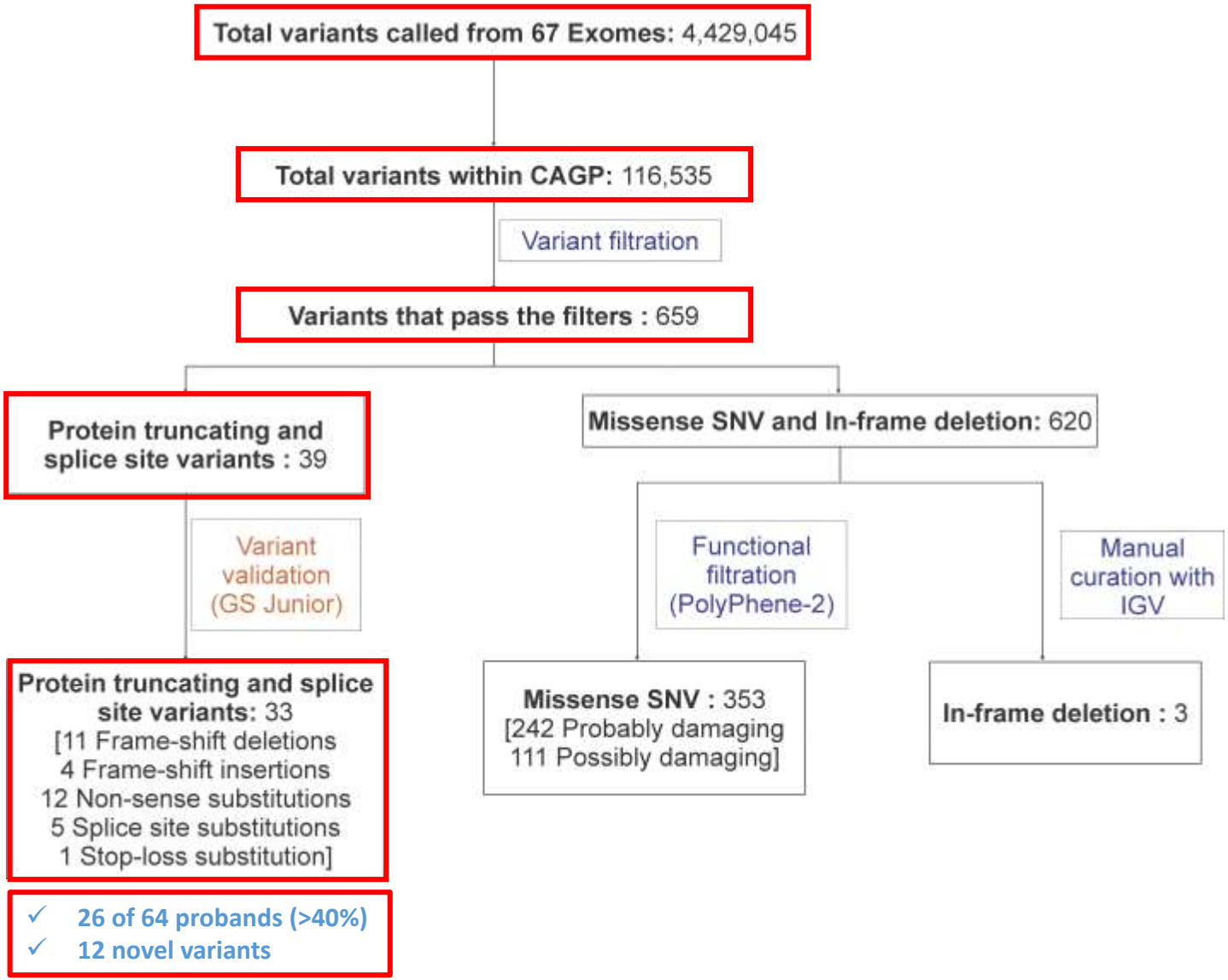
Breadth of target coverage >=10X:

- ✓ **96%**(85%-98%)

Depth of target coverage:

- ✓ **107X** (61X-297X)

Results


Total variants called from 67 Exomes: 4,429,045
Total variants within CAGP: 116,535
Variant filtration
Variants that pass the filters : 659
Protein truncating and splice site variants : 39
Missense SNV and In-frame deletion: 620
Variant validation (GS Junior)
Functional filtration (PolyPhene-2)
Manual curation with IGV
Protein truncating and splice site variants: 33
[11 Frame-shift deletions
4 Frame-shift insertions
12 Non-sense substitutions
5 Splice site substitutions
1 Stop-loss substitution]
Missense SNV : 353
[242 Probably damaging
111 Possibly damaging]
In-frame deletion : 3
✓ 26 of 64 probands (>40%)
✓ 12 novel variants

Results

Known breast cancer predisposing genes

Gene Name	Variant Frequency (ExAC03)	rsID (dbsnp147)
PALB2	-	-
BARD1	3,77E-05	rs587780021
CHEK2	1,80E-03	rs555607708
RAD51C	2,83E-05	rs754525165
FANCI	9,43E-06	rs149464307
FANCA	-	-
RECQL4	2,00E-04	rs386833845
RECQL4	-	-
RINT1	-	-
ABCC11	-	-
ABCC11	6,00E-04	rs145048685

Candidate breast cancer predisposing genes

Gene Name	Variant Frequency (ExAC03)	rsID (dbsnp147)
EXO1	1,80E-03	rs4150000
ALKBH2	-	-
CCNH	-	-
MUS81	-	-
TDP1	9,44E-06	rs762302264
DCLRE1A	2,60E-03	rs41292634
DCLRE1C	1,01E-05	rs121908156
PDE11A	1,20E-03	rs573163079
PDE11A	2,90E-03	rs76308115

Associated with different hereditary syndromes

Gene Name	Variant Frequency (ExAC03)	rsID (dbsnp147)
BBS10	7,00E-04	rs549625604
BBS10	-	-
CD96	1,88E-05	rs766366613
CD96	9,43E-05	rs201691670
CYP1A1	8,00E-04	rs561096394
DNAH11	-	-
ESCO2	-	rs80359856
FLT4	-	-
HPS6	3,00E-04	rs200206362
MYH8	1,10E-03	rs144321381
NME8	7,56E-05	rs538425312
NME8	4,00E-04	rs142525551
TTC8	-	-

"-" = Not available

Conclusions

- ✓ *Deep sequencing enabled* us to detect known/novel protein truncating & splice site variants in > *40% of BRCAX families.*

- ✓ Damaging mutations were found in *established breast cancer predisposing genes* not yet routinely screened. This information can be used for *preventive counseling and /or patient selection* for therapeutic trials with PARPi (e.g. RAD51C)

- ✓ Damaging mutations in *genes not yet validated as breast/ovarian cancer predisposing genes* were also found. These genes are in the process of:
  - *Segregation analysis in the concerned families*
  - *LOH* studies
  - Transversally looked in all *unresolved families* in our database

- ✓ In addition, *in-frame deletions* and *missense* substitutions predicted as "probably/possibly damaging" by PolyPhene-2 were also detected.

Acknowledgement

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ORC Oncology Research Centre

Laboratory of Medical and Molecular Oncology

Prof Dr. Jacques De Greve
Dr. Erik Teugels
Dr. Sylvia DeBrakeleer and colleagues

BRIGHT care

Prof. Dr. Sonia Vandooren
Dr. Didier Croes
Ir. Ben Caljon and colleagues

Thank You !