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Institute of Human Genetics

Zentrum für erbliche Tumorerkrankungen

CIO Centrum für Integrierte Onkologie Köln Bonn

Exome sequencing identified potentially causative genes for serrated polyposis syndrome (SPS)

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Genetics of SPS: state of affairs

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- **Truncating** variants in ***RNF43***
    - 2/20 unrelated patients: p.(Arg113*) (Gala et al.)
    - 1 familial case: p.(Arg132*) (Taupin et al.)
    - 1/4 families: c.953-1G>A (Yan et al.)
- **Truncating** variants in 5 regulators of **oncogene-induced senescence (OIS)** in 5/20 individuals (OR=3.0; 95% CI, 0.9–8.9; P=.04) (Gala et al.)
- Few patients with *MUTYH* variants

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- **Etiology of the syndrome not identified in the vast majority of patients**

Clinical characteristics of patient cohort

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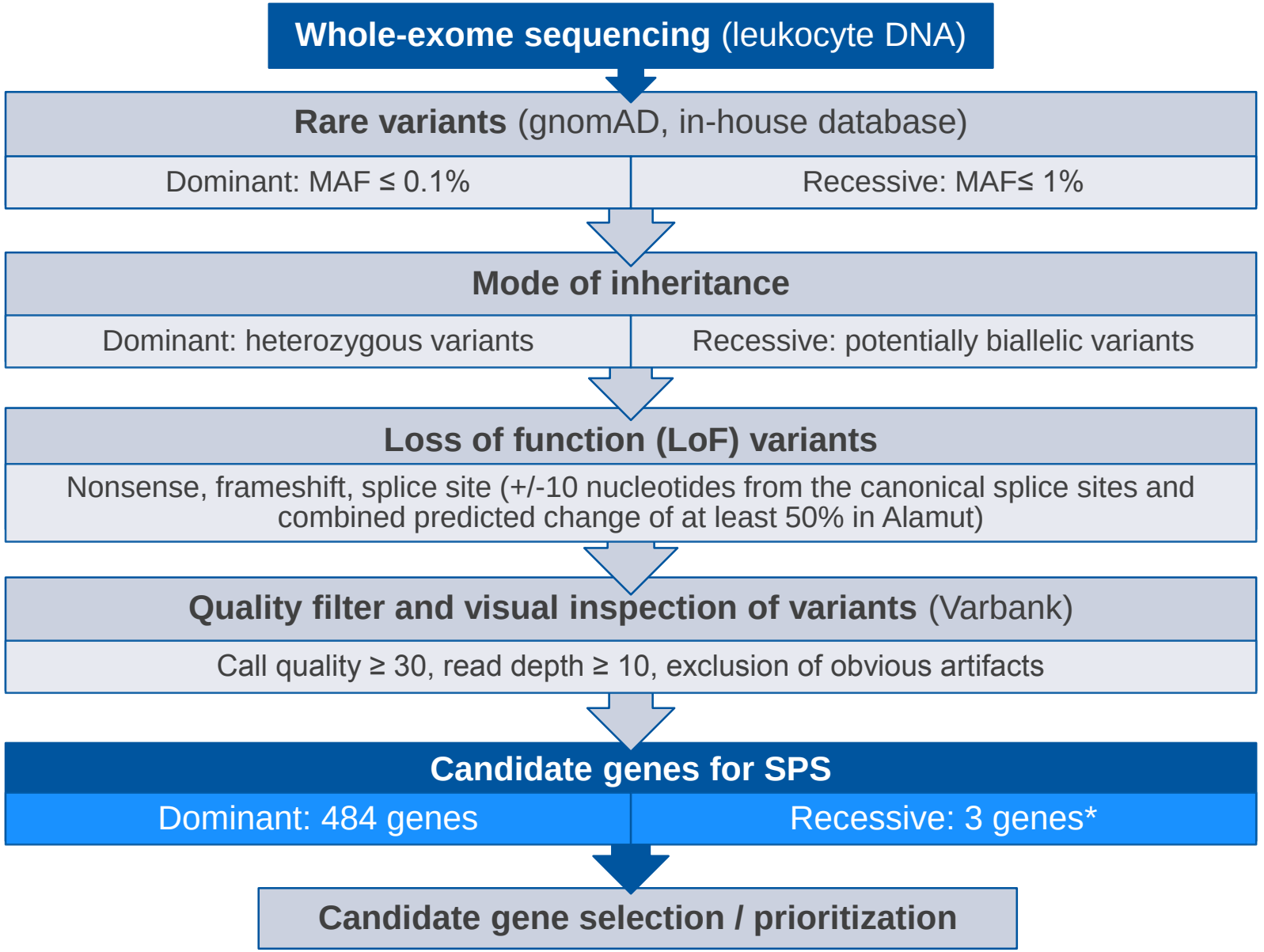
	No. of patients
Index patients	**49**
Gender (female/male)	35/14
Mean age at diagnosis (years)	**39**
Range (years)	14-67
No. of serrated / hyperplastic polyps	
< 20	4 (8%)
≥ 20	**40 (82%)**
multiple	5 (10%)
Colorectal cancer (CRC)	7 (14%)
Family history	
1° relative or sibling with CRC or polyps	**24/49 (49%)**
Sporadic	9/49 (18%)
Unclear	16/49 (33%)

Study Design: Filter steps



* Preliminary data: biallelic state has not been confirmed yet

Study Design: candidate gene selection criteria

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Function / Pathway	• Apoptosis • Canonical wnt signaling • Cell cycle control • DNA damage response • DNA repair
Gene Lists	• Tumor suppressor genes • Downregulated in colorectal cancer • Mutated in serrated pathway
LoF intolerance	• pLi score ≥ 0.9
Recurrently mutated	• Variants in ≥ 2 patients • Biallelic variants

Results: recessive model

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Gene	Pat ID	Germline Variant	Function/Pathway	gnomAD (AF)
Genes with potentially biallelic truncating variants				
FAM184B	136	c.1030+1G>A	Protease inhibitor	0.00001
GBP3	3	c.2287delT;p.(Ser763Leufs*4)	Microtubule-associated motor protein	0
PCDHGB1	123	c.1067_1068insT; p.(Arg356Serfs*3)	Transcriptional regulation	0.00007

Results: dominant model

Gene	Pat ID	Germline Variant	Function/Pathway	pLi
Genes involved in wnt signaling pathway				
DLG1	45	c.2104+1G>C	Multi-domain scaffolding protein; downregulated in CRC	1
IFT80	27	c.1258C>T;p.(Gln420*)	Part of the intraflagellar transport complex B	0
PPP2R1B	34	c.1957C>T;p.(Gln653*)	Putative tumor suppressor	0
	45	c.343_344delGT; p.(Val115Cysfs*3)		

Results: dominant model

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Gene	Pat ID	Germline Variant	Function/Pathway	pLi
Genes involved in DNA repair / DNA damage response				
CHEK2	33	c.902T>A;p.(Leu301*)	Cycle checkpoint regulator	0
	16	c.444+1G>A		
CINP	71	c.628C>T;p.(Arg210*)	Cycle checkpoint regulator	0
EXO1	45	c.1965delG;p.(Ser656Alafs*79)	Mismatch repair, double-strand break repair	0
FAN1	61	c.2489-1G>C	DNA interstrand cross-link repair	0
FANCG	69	c.313G>T;p.(Glu105*)	Postreplication repair or a cell cycle checkpoint regulator	0
POLQ	145	c.2516delT; p.(Phe839Serfs*26)	Double-strand break repair	0
RAD23A	48	c.72+5G>T	Nucleotide excision repair	0
RAD9A	145	c.245_248delCTGT; p.(Val83Serfs*18)	Cell cycle checkpoint regulator	0
TELO2	113	c.1822C>T;p.(Gln608*)	Cell cycle checkpoint regulator	0
TEX15	113	c.7221dup;p.(Tyr2408Ilefs*8)	DNA double-strand break repair	0
USP51	45	c.7delC;p.(Gln3Argfs*54)	DNA double-strand break repair	0.9

Results: dominant model

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Gene	Pat ID	Germline Variant	Function/Pathway	pLi
Genes with a cancer-associated function and a pLi-score ≥ 0.9				
CAMTA2	11	c.3540-8C>G	Transcription activator. May act as tumor suppressor	1
FURIN	71	c.1792+4A>C	Ubiquitous endoprotease; mediates processing of TGFB1, an essential step in TGF-beta-1 activation	1
LARP4	79	c.416G>A;p.(Arg139Gln)†	Regulation of cell morphology and cytoskeletal organization	1
PCDH20	93	c.2132G>A;p.(Trp711*)	Cell-adhesion protein	0.9
SAMD4B	13	c.365_366delGT; p.(Ser122Thrfs*34)	Transcription repressor	1
SSH2	12	c.3802C>T;p.(Arg1268*)	Protein phosphatase	1
TJP1	124	c.1225_1228delCCTA; p.(Pro409Ilefs*13)	Cell migration	1

† exonic splice site variant

Results: dominant model

Gene	Pat ID	Germline Variant	Function/Pathway	pLi
Genes mutated in more than 2 patients				
ZSCAN29	3	c.523G>A;p.(Gly175Arg)†	May be involved in transcriptional regulation	0
	139	c.2074C>T;p.(Arg692*)		
	69	c.2469_2470delTG; p.(Cys823Trpfs*2)		

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Summary and Outlook

- **Exome sequencing in 49 SPS patients**
- Identification of **new potentially causative genes for SPS**
  - potentially biallelic truncating variants
  - recurrently mutated
  - LoF intolerant
  - tumorigenesis-associated function
- Considerable **genetic heterogeneity**

Summary and Outlook

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- **Exome sequencing in 49 SPS patients**
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- Considerable **genetic heterogeneity**
- **Current work-up:**
  - validation of variants by Sanger sequencing
  - inclusion of **missense variants** and **CNVs**
  - **testing segregation** with the phenotype where applicable
  - **exome analysis of further 37 SPS patients**
  - **pathway analysis**
  - **burden** tests
  - **oligogenic** analysis

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