

# MYH-associated Polyposis (MAP)

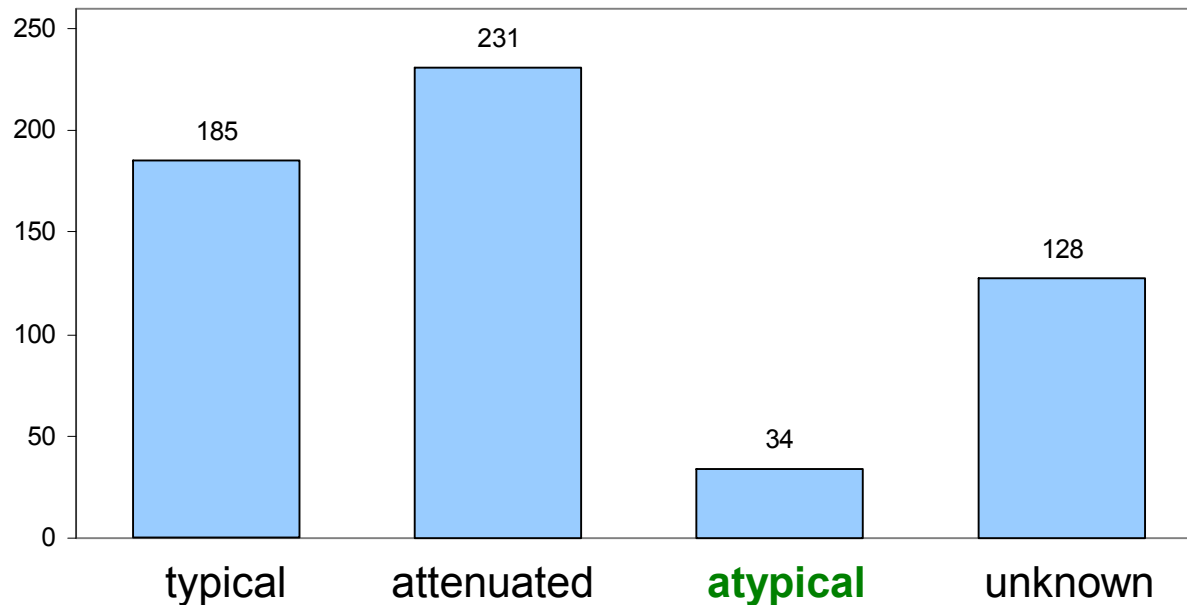
Frequency, mutation spectrum and phenotype in 267 German patients with multiple colorectal adenomas

Stefan Aretz

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# FAP/AFAP patients Bonn

- 585 patients screened for **APC** germline mutations (PTT, DHPLC, MLPA)
- mutation detection rate: 287 (49 %)

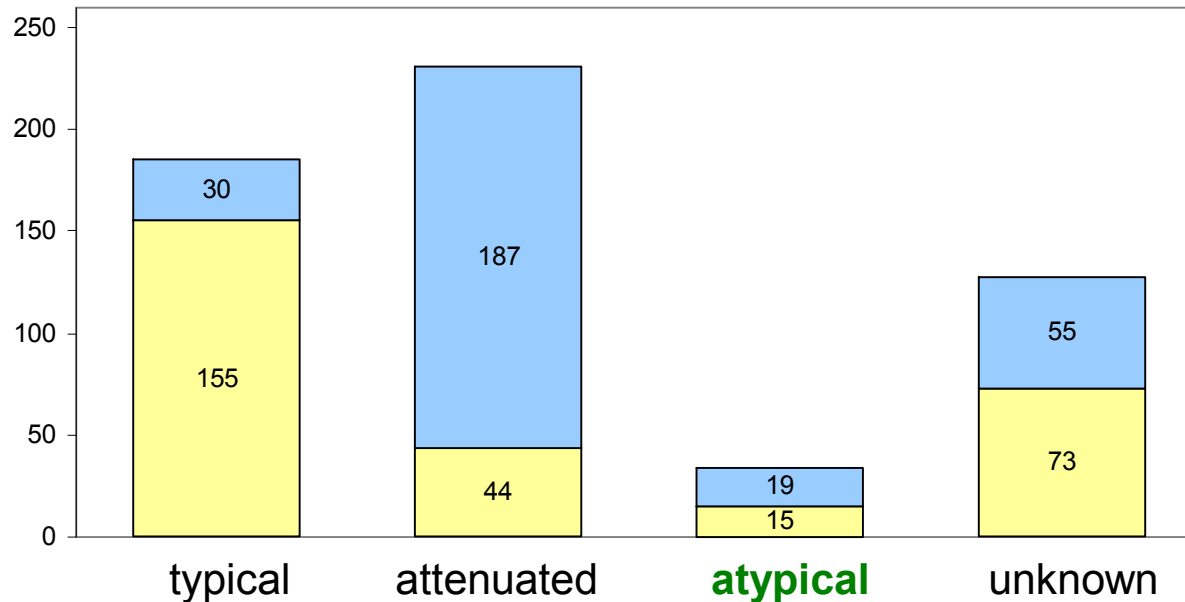


phenotypes in 585 unrelated patients

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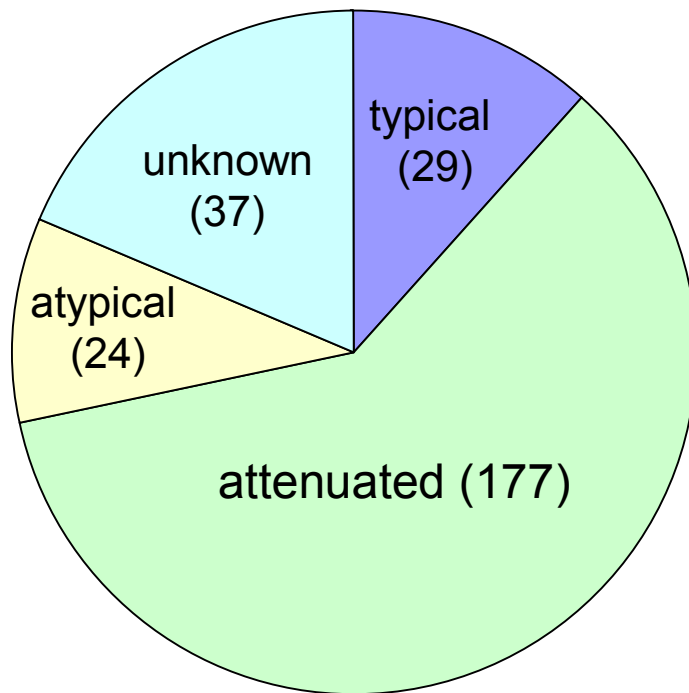
APC mutation detection rates



phenotypes in 585 unrelated patients

# MYH screening - patients

- 267 unrelated, unselected APC negative patients
- **MYH** screening (sequencing of the whole coding region)



phenotype in  
267 APC negative  
patients

116 normal controls (Heike Görgens, Dresden)

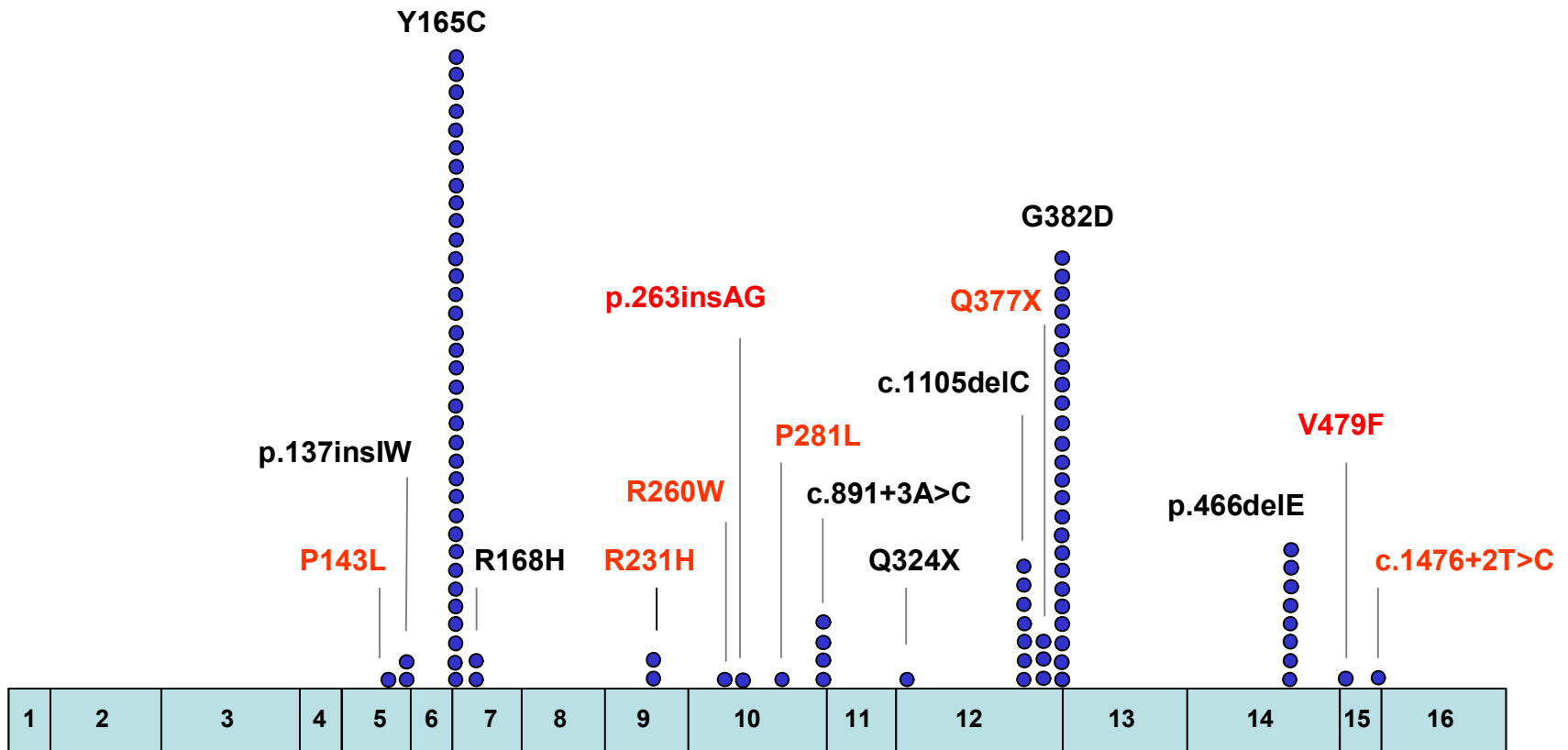
## MYH - biallelic mutations (Bonn)

**biallelic mutations: 47 patients (18 %)**

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**biallelic mutations:**

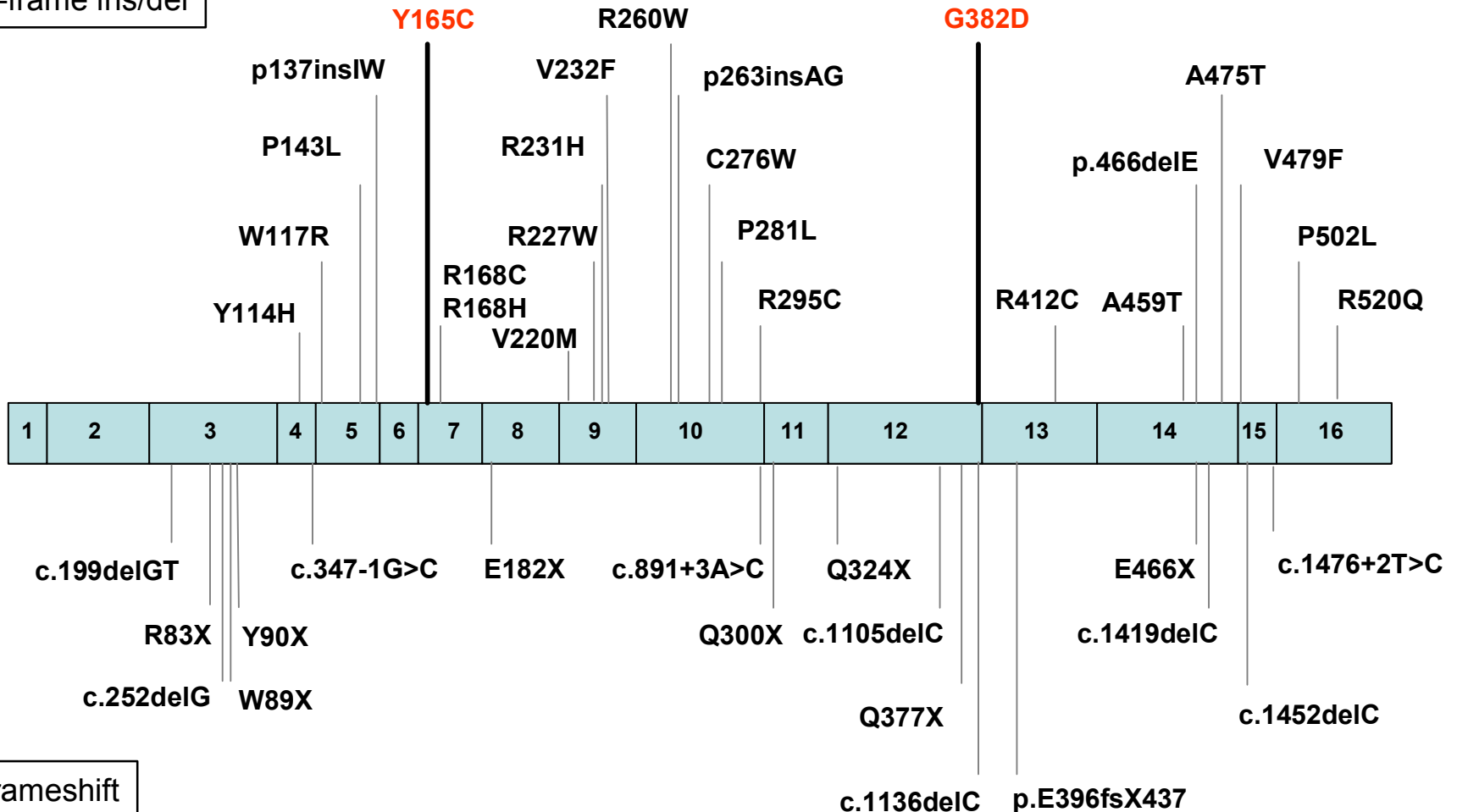
**47 patients (18 %)**



all missense mutations at highly conserved sites  
(except R260W and V479F)

# MYH mutation spectrum - biallelic mutations

Missense  
In-frame ins/del



Frameshift  
Nonsense  
Splice site

# MYH mutations

## „Hot spots“

- biallelic Y165C and/or G382D 47 %
- Y165C or G382D comp.-heterozygous 32 %
- neither Y165C nor G382D 21 %

# MYH mutations

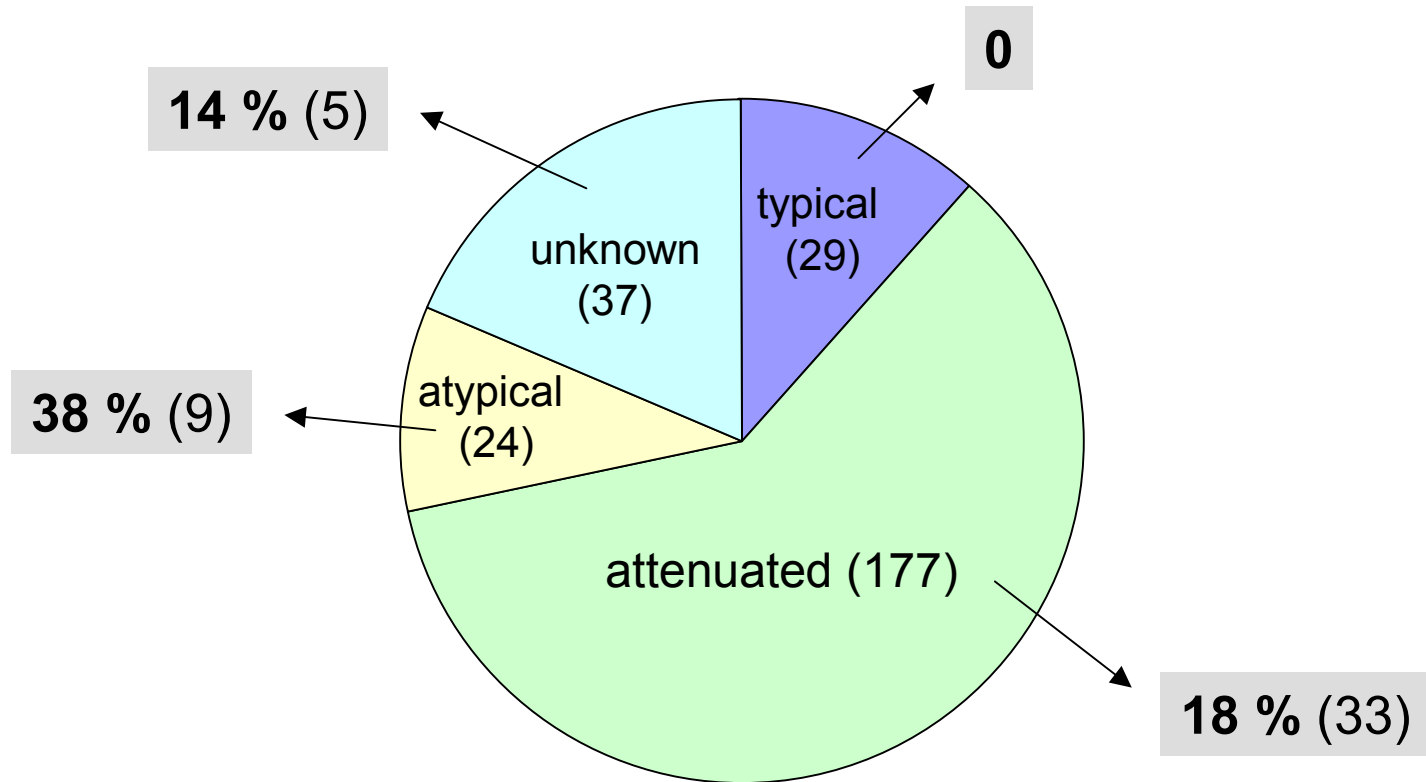
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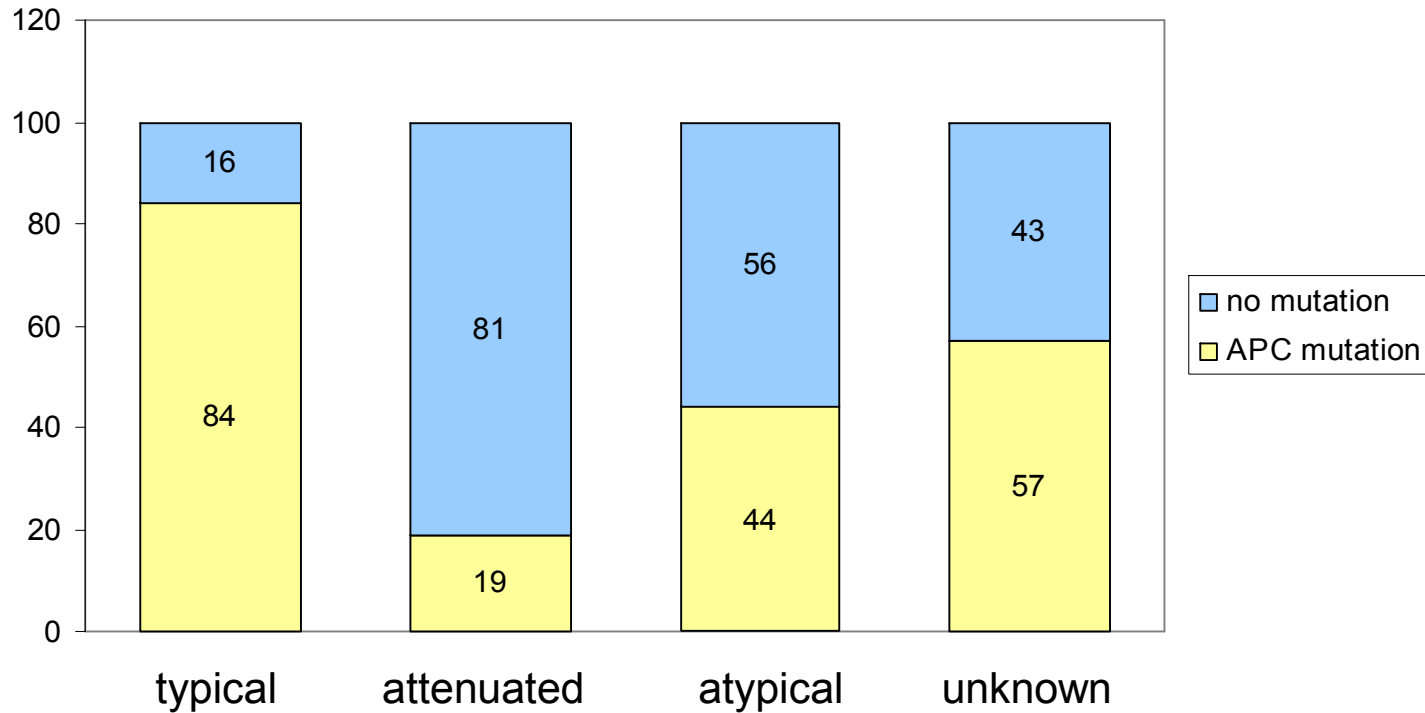
## 116 normal controls

- Y165C + G382D: allele frequency each 0.43 %
- no other variants

# Biallelic MYH mutations

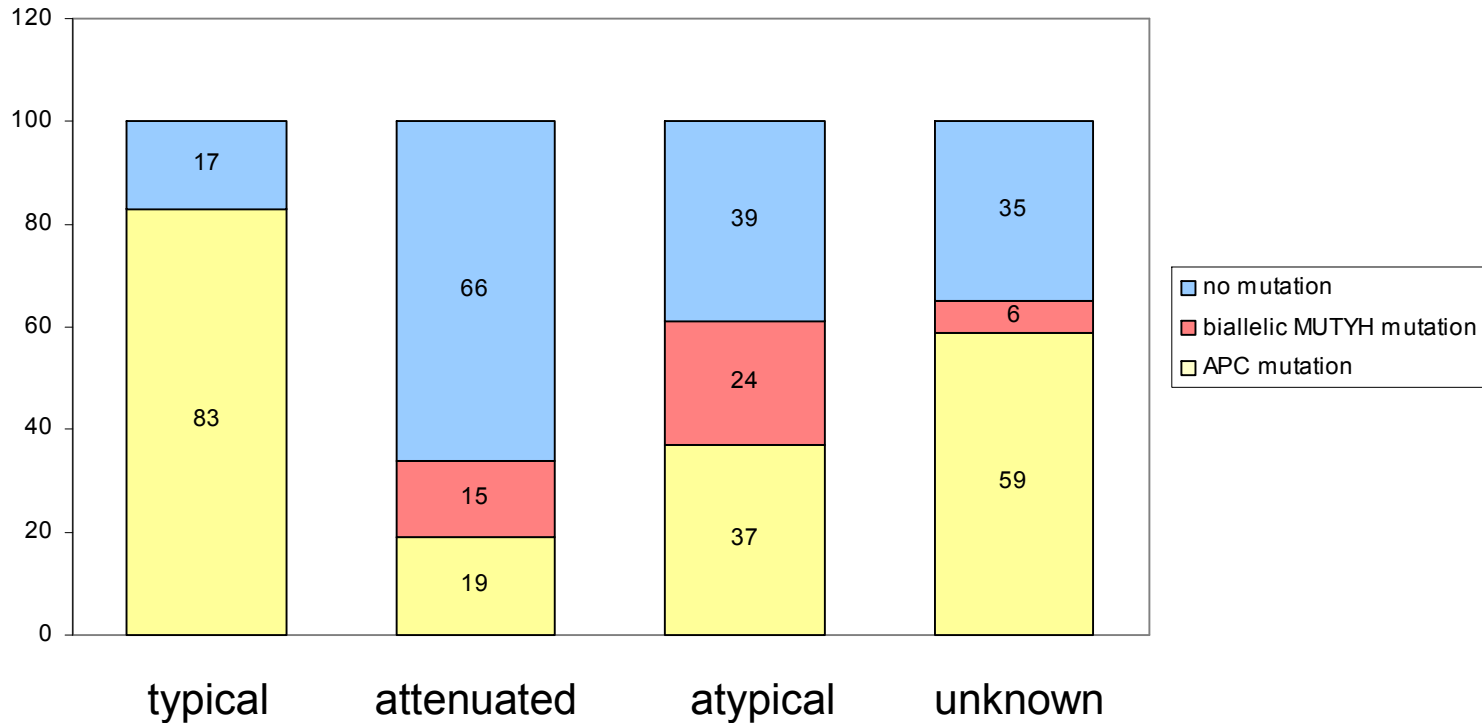


# Incidence APC mutations



Phenotypes in 585 unrelated patients

# Incidence biallelic MYH mutations



phenotypes in 585 unrelated patients

**MYH almost doubles the mutation detection rate in cases with attenuated course**

# Polyp number – biallelic MYH mutations

Phenotype (polyp no, CRC)	biallelic MYH	mean age at diagnosis MAP	author
<b>15-100</b>	<b>16-42 %</b>	<b>56, 49, 44</b>	Sieber 2003; Gismondi 2004; Wang 2004; Venesi0 2004
<b>&gt;100</b>	<b>7-19 %</b>	<b>49, 49, 54</b>	Sieber 2003; Gismondi 2004; Wang 2004
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<b>15-100</b>	<b>25 %</b>	<b>42</b>	<b>own data</b>
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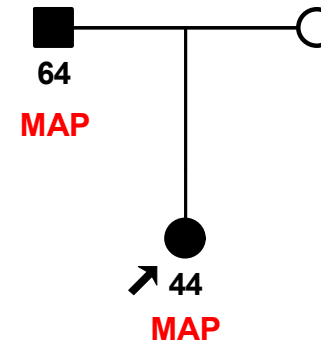
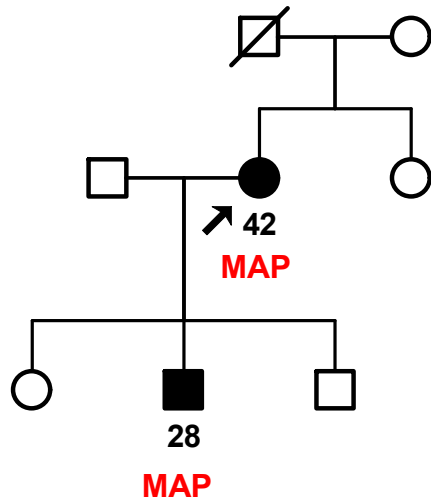
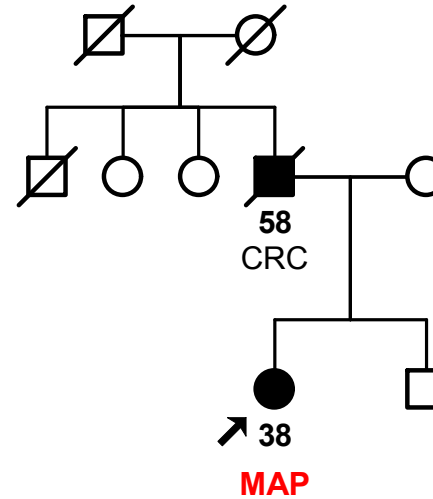
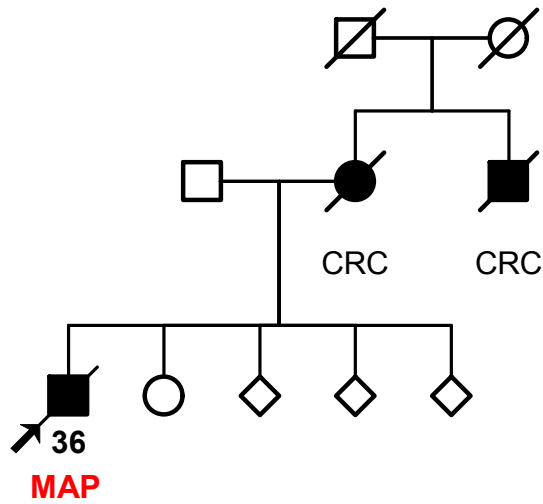
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most characteristic MAP feature: advanced age at diagnosis

# MAP - phenotype

<b>mode of diagnosis</b>	<b>87 % with symptoms</b>
<b>mean age at diagnosis (years)</b>	<b>44 (24-68)</b>
<b>colorectal adenoma number</b>	<b>20 to a few hundreds</b>
<b>proximal adenoma distribution</b>	<b>44 %</b>
<b>colorectal phenotype</b>	<b>attenuated (80 %) atypical (18 %)</b>
<b>CRC at diagnosis</b>	<b>53 %</b>
<b>duodenal polyposis</b>	<b>24 %</b>
<b>extraintestinal lesions</b>	<b>no</b>
<b>mode of inheritance</b>	<b>31 autosomal recessive 7 vertical</b>

# Pedigrees with vertical transmission



# Monoallelic variants in the coding region

<b>heterozygosity frequency</b>	<b>No.</b>	<b>%</b>
general population		<b>1-2</b>
our 267 patients	9	<b>3.4</b>
<b>variants with functional relevance</b>	<b>3</b>	<b>1.1</b>
silent changes	4	1.5
missense variants unconserved sites	2	0.8

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phenotype: more in line with typical FAP

**no evidence for heterozygosity effect**

## Conclusions: MYH mutation screening

- not successful in patients < 15 adenomas  
in patients with typical FAP
- the whole gene has to be screened, if no hot-spot mutation is identified
- also in pedigrees with two affected generations
- recurrence risk: low in children of MAP patients (about 1-1.5 %)

## Conclusions: counselling and surveillance

- to date no specific screening guidelines
- colorectal surveillance as advised in AFAP:  
annual colonoscopy, starting at 18-20 years
- predictive testing in siblings and children  
at about 18-20 years of age
- intensive colorectal screening should be  
restricted to biallelic mutation carriers and to  
siblings

## Open questions

- specific colorectal surveillance for monoallelic carriers ?
- extent of duodenal surveillance ?

# Acknowledgements



## Project

*„Clinical and genetic characterisation of patients with multiple adenomatous polyps“*

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Hans K. Schackert**

# Tumour predisposition syndromes and colorectal adenomatous polyps

## HNPCC

- few adenomas
- early CRC
- microsatellite instability (MSI)
- extracolonic tumours
- MLH1, MSH2, MSH6
- autosomal-dominant

## AFAP

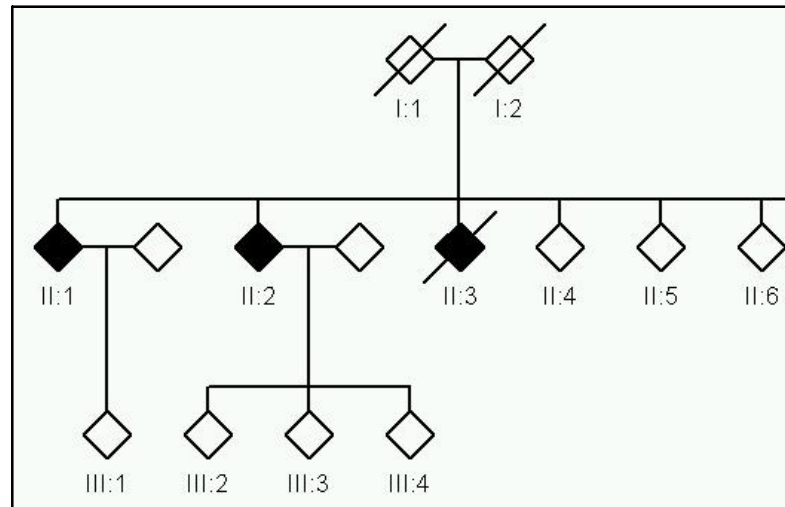
- 10-100 adenomas
- later onset
- other tumours uncommon
- no MSI
- APC: 20-30 %
- often sporadic
- heterogeneous

## FAP

- 100 – thousands adenomas
- second decade
- early CRC (100 %)
- duodenal polyposis
- extraintestinal lesions
- APC: 80-90 %
- autosomal-dominant

# Multiple colorectal adenomas (MCA)

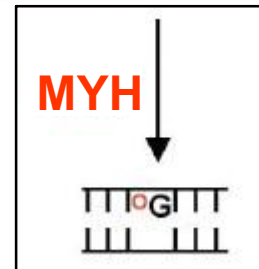
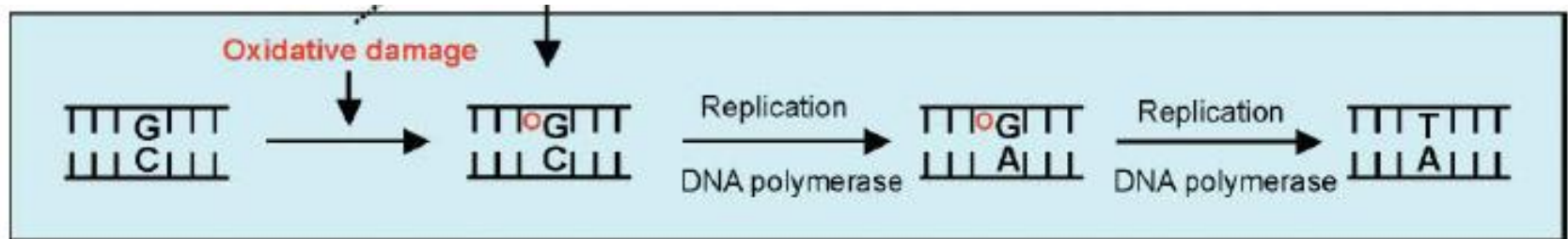
Al-Tassan et al., Nature Genetics, Feb 2002



- II:1 50 colorectal adenomas (50 years)
- II:2 50 colorectal adenomas (46 years)
- II:3 CRC + at least 1 adenoma (46 years)

Tumours: high frequency (83 %) of G:C > T:A transversions in APC

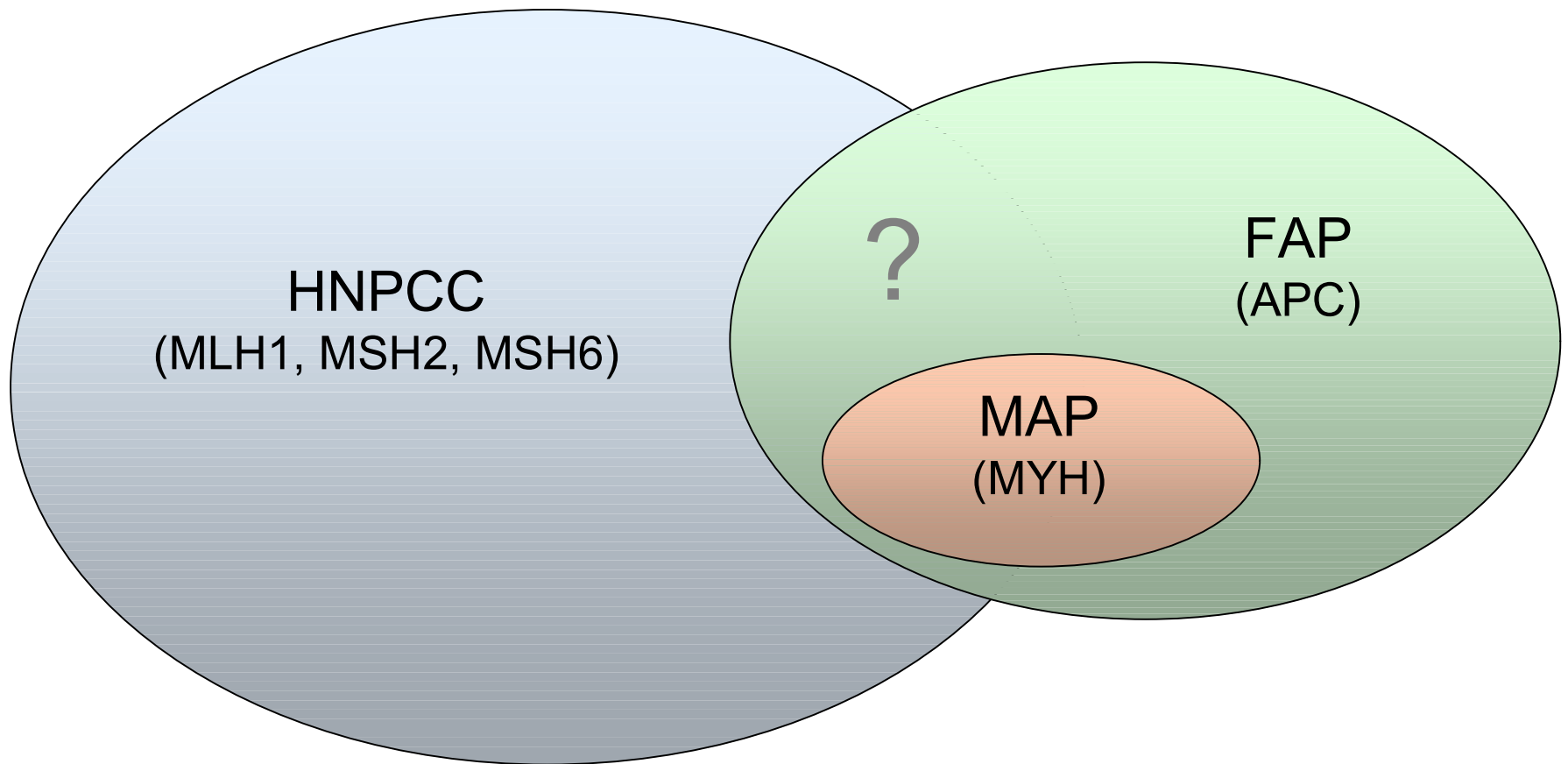
# MYH (MUTYH) gene



Cheadle et al., HMG, 2002

- base excision repair (BER)
- 1p35, 16 exons
- protects against mutagenesis caused by oxidative DNA damage (**8-oxoG**)
- MYH: excision of adenine mismatched with 8-oxoG
- MYH biallelic mutations increase **somatic G:C>T:A transversions** in other genes like APC
- MYH-associated Polyposis (MAP)
- **autosomal-recessive inheritance**

# Differential diagnosis multiple colorectale adenomatous polyps



## Polyp number – biallelic MYH mutations

Phenotype (polyp no, CRC)	mean age at diagnosis (y)	no. patients	biallelic MYH mutations	%	author
<b>15-100</b>	52-56, ?	12-37	5-8	<b>16-42</b>	Sieber 2003; Gismondi 2004; Wang 2004; Venesio 2004
<b>&gt;100</b>	30-40, ?	21-107	4-8	<b>7-19</b>	Sieber 2003; Gismondi 2004; Wang 2004
<b>1-10</b>	61, ?	40-306	0-4	<b>0-1.3</b>	Sampson 2003; Gismondi 2004; Wang 2004; Eliason 2005
<b>CRC &lt; 50 y</b>	< 50	116-358	0-2	<b>0.6-1.7</b>	Fleischmann 2004; Wang 2004
<b>CRC &gt; 50 y</b>	>50	328	0	<b>0</b>	Wang 2004;
<b>controls</b>		3600	0	<b>0</b>	Croitoru 2004; Wang 2004; Eliason 2005; Fleischmann 2004; Enholm 2003

phenotype (polyp no.)	mean age at diagnosis (y)	no. patients	biallelic MYH mutations	%	mean age at diagnosis MAP	author
<b>1-15</b>	<b>42</b> (5-59)	16	0	<b>0</b>		<b>own data</b>
<b>15-100</b>	<b>46</b> (6-76)	56	14	<b>25</b>	<b>42</b> (24-60)	
<b>&gt;100</b>	<b>45</b> (20-71)	45	9	<b>20</b>	<b>49</b> (37-68)	
<b>multiple</b>	<b>42</b> (11-65)	54	9	<b>17</b>	<b>42</b> (28-55)	
<b>unknown</b>	<b>41</b> (11-72)	96	15	<b>16</b>	<b>48</b> (39-55)	

most characteristic MAP feature: advanced age at diagnosis 30

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