DISTINCT SPECTRUM OF *APC* GERMLINE MUTATIONS IN FAMILIAL ADENOMATOUS POLYPOSIS AT THE CENTER-SOUTH OF PORTUGAL: IDENTIFICATION OF A MUTATIONAL HOTSPOT AND SUGGESTION OF A FOUNDER EFFECT

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Introduction: Familial adenomatous polyposis (FAP) is caused by *APC* germline mutations. These have been reported in classic and attenuated FAP (AFAP) but only two hotspots were described (codons 1309 and 1061-range:0-15%). We aimed to characterize the *APC* mutation spectrum in a FAP/AFAP population from the familial polyposis registry of the Portuguese Oncology Institute in Lisbon. **Methods:** We performed mutation analysis in 95 index patients from our FAP/AFAP cohort (61 FAP; 34 AFAP) using PTT, DGGE, sequencing and MLPA. Haplotype analysis was performed using 3 microsatellite markers flanking *APC* and 2 intragenic SNPs in 12 families with an intron 9 mutation (6 from our registry, 2 from INSA and 4 from IHG), occasionally detected in the literature, in order to evaluate a possible founder effect. All samples were anonymized. Statistics: Fisher's exact and X^2. **Results:** *APC* mutations were found in 47/61(77%) FAP and in 12/34(35%) AFAP families. The 1309del and 1061del contributed for 6/59(10%) and 2/59(4%) of the families, respectively. Exon 15 mutations were more frequent in FAP than in AFAP [30/47(64%) vs 1/12(8%),P<0.001]. A high mutation frequency was also found in exon 9 and flanking regions (9/59;15%), contributing for the majority of AFAP with *APC* mutation (8/12;67%). An intron 9 mutation (c.1312+3A>G) was highly represented (6/59,10%), exclusively in AFAP (6/12;50%). Segregating with this mutation, we detected a common haplotype apparently shared by 6 families. For D5S346, the common allele segregating with this haplotype was more frequent in the index patients (11/20;46%) than in a control population (20/90;22%). **Discussion:** We identified a specific distribution of *APC* mutations and a mutational hotspot in our population. The higher frequency of the c.1312+3A>G mutation in Center-South Portugal suggest a non-uniform distribution which may be explained by a founder effect. Further studies using SNPs flanking intron 9 and the analysis of more families/relatives are needed.