Founder effect in Lazio for Spinal and bulbar muscular atrophy (SBMA)

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And the Lazio Kennedy Study Group

Introduction: Spinal and Bulbar muscular atrophy (SBMA) is an adult-onset, X-linked, disorder, caused by expansion of a polymorphic CAG in the androgen-receptor (AR) gene (1). Although relatively frequent only a few large families have been reported allowing for intrafamiliar variability assessment.

Aim To investigate a large series of patients originating from the same restricted area of Southern Lazio and compare them to other patients living in other areas of the region

Materials and methods Over the last years several men were diagnosed with SBMA, who could trace their ancestry in the small city of Ferentino (20.000 inhabitants) in South-East Lazio. We decided to look for additional patients referred to other neurological centers through a network of investigators named Lazio Kennedy Study Group. We genotyped all patients and some maternal relatives to identify shared haplotypes. 4 polymorphic microsatellites (DXS1213, DXS1194, DXS1111,DXS135) flanking the expanded CAG sequence have been analyzed. Moreover we genotyped patients with genetically confirmed diagnosis of SBMA originating from other areas of the Lazio.

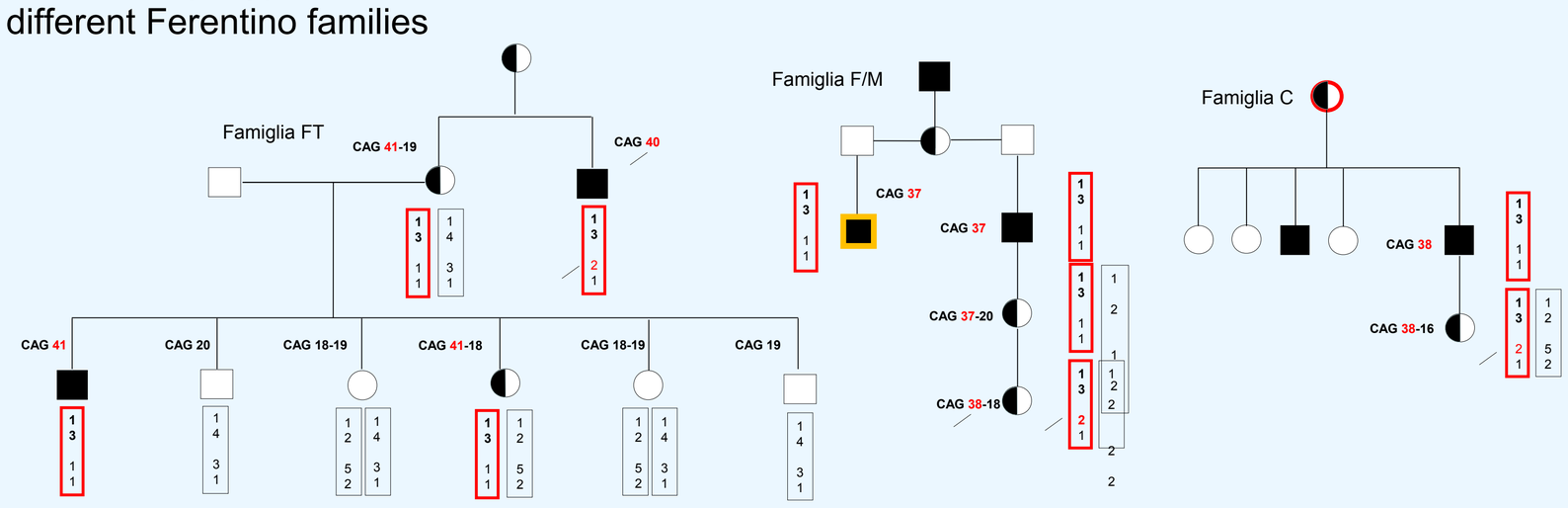
	Viventi	Studiati	Deceduti	Totale
Maschi affetti	13	12	6	19
Femmine portatrici	18	18	10	28
				47

Xq11.2-q12

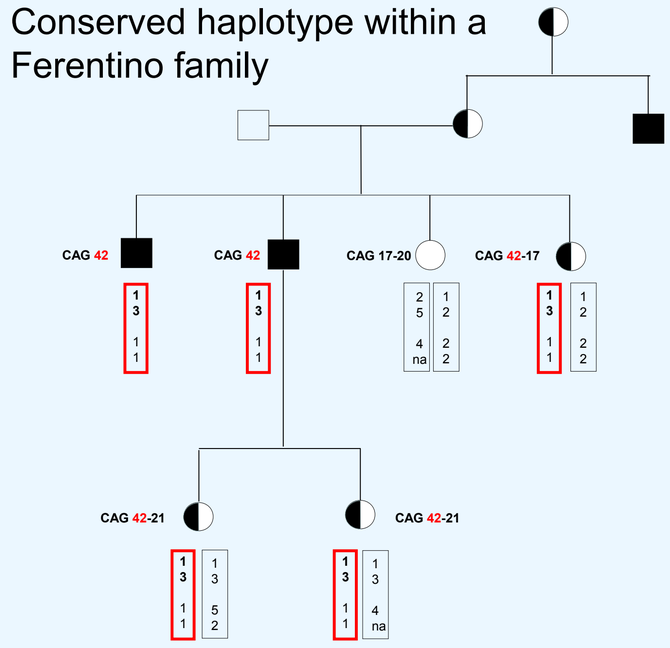
Common “Ferentino” haplotype

DXS1213	1	239	Shared haplotype through families
DXS1194	3	137	
AR/SMAX1			No obvious family relationship
			Deep ancestry
DXS1111	1	121	Founder effect
DXS135	1	226	

Variable haplotype within different Ferentino families



Conserved haplotype within a Ferentino family

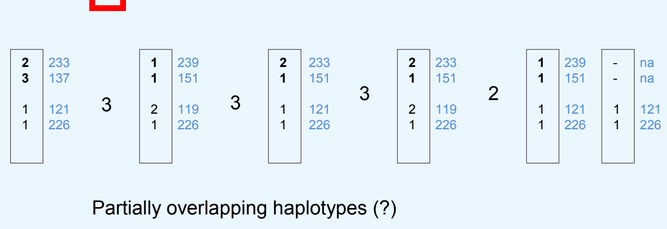


Results:

- So far 19 patients have been identified originating from Ferentino. Upon detailed reconstruction of the family trees through direct interviews, no clear recent shared relationship among patients could be ascertained, apart for a couple of brothers and a couple of maternally related cousins, while upon extensive search of the commuity archives, only two families could be traced to a common female ancestor living around 1860. The patients were aged 46-77 years, the CAG expansion was in the lower range for the disease (disease associated repeats 37-62; normal values 10-36); their clinical status ranged from mild initial to severe late disability with 2 wheelchair-bound patients. In one case a retrospective diagnosis was made possible by a video clip of an elderly man, who had died more than 20 years ago, with clear evidence of facial weakness as well as swallowing difficulties. All 18 patients from Ferentino carried an identical haplotype.
- Within families we observed examples of retained conserved haplotypes over generations or examples of varying haplotypes within families over a few generations suggesting relatively high variability of the microsatellites used.
- Additional 15 SBMA patients from the Lazio regions carried either identical haplotypes /2) or partially overlapping haplotypes

Conclusions We identified a cohort of patients with SBMA from the same restricted area, likely representing the largest series so far described in Italy and elsewhere (2,3). We identified a shared haplotype in all patients from Ferentino and additional ones form nearby areas suggesting an even deeper founder effect. Such an extended series of patients provides the ideal background for detailed assessment of genotype-phenotype correlations and intrafamilial variability.

Haplotypes from additional 15 SBMA patients from Lazio



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