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Genetic ancestry analysis of the Italian founder population carrying the cardiac amyloidosis-causing variant Val122Ile in the transthyretin gene

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Background: Transthyretin amyloidosis is a life-threatening disorder caused by the deposition of TTR amyloid in various tissues and organs. The most common worldwide pathogenic variant with almost exclusive cardiac involvement is Val122Ile (rs76992529), with an allele frequency of 3.5% in the U.S. African-American population, but rare in Caucasians. Unexpectedly, we identified 23 Caucasian individuals with Val122Ile in our amyloidosis referral center (9 affected patients, 14 carriers), belonging to 9 unrelated families.

Purpose: To determine the ancestral origin of the Tuscan founder population of TTR Val122Ile carriers.

Methods: A total of 24 individuals were included in the analysis (our 23 probands and relatives from Val122Ile families and the Caucasian reference sample NA10851 (CEU – Utah resident with European ancestry). All samples were genotyped using the EUROFORGEN Global AIM-SNP array1, inclusive of 127 highly informative SNPs to infer genetic ancestry. We have performed a principal component analysis (PCA) of the 9 unrelated probands and NA10851, compared with the Phase 3 of the 1000 Genomes Project data, comprising 2504 unrelated individuals from >20 distinct populations.(Figure 1).

Results: As shown in Figure 1, all our samples but one (from Argentina) cluster very close to the super-cluster of European populations, and distant from the populations of African ancestry. The proband from Argentina and the Caucasian reference sample NA10851 cluster close to Mexicans and Peruvians, and the super-cluster of European populations, respectively, confirming the robustness of the analysis.

Conclusion: Based on this result, we can confidently conclude that our samples from Tuscan families in which the TTR Val122Ile variant segregates are of ancestral European origin, with no mixed African ancestry, implying that the same variant originated in Africans and Europeans independently and not as result of genetic admixture. These findings suggest the presence of a mutational hot spots in TTR, with potential impact on the epidemiology of amyloidosis worldwide.

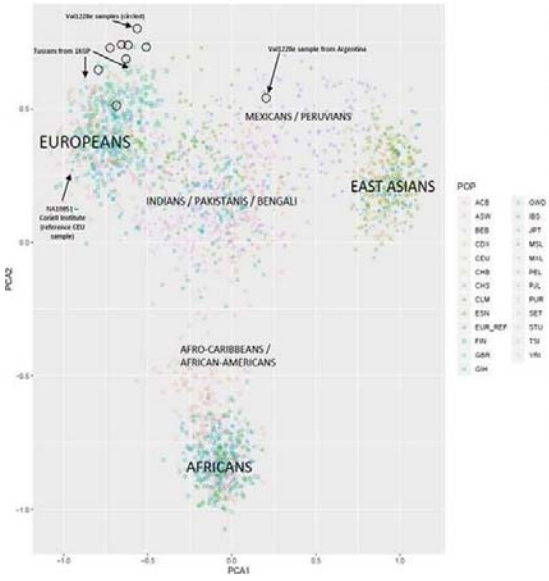

Figure 1 – PCA performed on the 9 unrelated probands from our sample set (SET, circled) with 23 distinct populations from the Phase 3 of the 1000 Genomes Project. ACB=African Caribbeans in Barbados; ASW=Americans of African ancestry in SW USA; BEB=Bengali from Bangladesh; CDX=Chinese Dai in Xishuangbanna, China; CEU=Utah Residents with Northern and Western European ancestry; CHB=Han Chinese in Beijing, China; CHS=Southern Han Chinese; CLM=Colombians from Medellin, Colombia; ESN=Esan in Nigeria; EUR_REF=reference sample NA10851 (CEU); FIN=Finnish in Finland; GBR=British in England and Scotland; GIH=Gujarati Indian from Houston, Texas; GWD=Gambian in Western Divisions in the Gambia, IBS=Iberian population in Spain; JPT=Japanese in Tokio, Japan; MSL=Mende in Sierra Leone; MXL=Mexican ancestry from Los Angeles, USA; PEL=Peruvians from Lima, Peru; PJL=Punjabi from Lahore, Pakistan; PUR=Puerto Ricans from Puerto Rico; STU=Sri Lankan Tamil from the UK; TSI=Tuscans from Italy; YRI=Yoruba in Ibadan, Nigeria.