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Letter to the Editor

Sample selection bias in an international DNA panel: Does Native American haplogroup Q-M3 has the b2/b3 deletion?

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For the past 10 years, the effect of Y chromosome microdeletions on spermatogenesis and its polymorphic characteristic has been a topic of debate. The influence and effect of Y chromosome haplogroups on the deletion's prevalence can be easily predicted from its haploidy and clonal transmission. The evidence of a 1.8-Mb deletion (b2/b3) detected in high prevalence among men from one specific branch of the Y genealogy, haplogroup (Hg) N, drove the attention to the association between haplogroups and constitutive deletions in the AZFc region of the Y chromosome [1]. Although the b2/b3 deletion removes 12 members of eight testis-specific gene families, it seems to have a modest influence on fitness, or its effect has been counterbalanced by another Y-linked factors. Repping et al. (2004) analyzed 326 samples from men with unknown spermatogenesis purchased from NHGRI/NIGMS DNA Polymorphism Discovery Resource (Coriell Institute, Camden, NJ, USA). From these samples, 21/21 samples from Hg N showed to be b2/b3-deleted, while the same deletion was also detected in Hgs F*(xHK) (1/18), I (1/38) and Q3 (2/9). Men belonging to Hgs F* and I had abnormal and normal spermatogenesis, respectively. Men belonging to Hg Q3 had unknown spermatogenic phenotype. All previously mentioned samples had the same organization of the AZFc region (G-R), as was shown by FISH analysis. By exhaustive characterization of 47 major branches of the Y genealogy, structural polymorphisms among human Y chromosomes have been described [2]. For this matter, the same DNA Polymorphism Discovery Resource has been employed and the results imply that both Hg N (N3 and N*) and Q3 harbor the same Y chromosomal architecture (c35) as well as the b2/b3 deletion.

Alike Hg N, which is found at high frequencies in northern Asia, the American continent is characterized by high frequencies of Hg Q-M3 among the native populations. In the urban population from South American countries, as Argentina, the prevalence of Hg Q-M3 is approximately 5% among the male population [3]. As the Argentinean extant population still conserves Native American Y-chromosome inheritance belonging to Hg Q-M3, its study is relevant for the prevalence and effect of Y-chromosome microdeletions in South American populations. In order to set up the deletion's screening in Native American populations, we purchased from Coriell Institute the samples previously analyzed by Repping et al. (2004 and 2006). Samples PD024 (NA15594) and PD066 (NA15503) were confirmed as carrying the b2/b3 deletion as well as belonging to Hg Q-M3. Nevertheless, these samples have been further analyzed by short tandem repeats (STRs) located within the euchromatic region of the Y chromosome, showing identical haplotypes in 23 markers, included in PowerPlex® Y23 (Promega). In order to deepen the analysis, we included 13 additional rapid mutating STRs (RM-STRs), which evidenced 12/13 identical alleles. The only inconsistency was in marker DYF403S1a due to a possible one-step mutation (mutation rate $= 3.10 \times 10^{-2}$) [4]. Additionally, these samples have been characterized by autosomal STR analysis using PowerPlex® Fusion (Promega), mitochondrial DNA (mtDNA) control region sequencing, and X-chromosome STRs by Investigator® Argus X-12 (Qiagen). The results obtained from the overall characterization are included in the Supplementary material. Taken together, the Y chromosome haplotype analysis implies that samples NA15594 and NA15503 belong to the same paternal lineage. Conversely, mtDNA discards an identical maternal lineage, being their haplogroups compatible with two different Native American lineages, both present in the US population (B4b and A2). Autosomal STRs excluded the hypothesis that these individuals have a first-degree parent–child biological relationship. Nevertheless, statistical analysis indicates that the donors to samples NA15503 and NA15594 are 1078 and 5570 times more likely to be full and half siblings sharing the same father, respectively, than being unrelated individuals. It is also worthy to notice that the sample NA15594 evidenced a triallelic pattern in marker D1S1656 sharing two allelic variants with the donor to the sample NA15503, which is extremely rare and could be explained considering that both DNA samples come from cell lines therefore with high mutation levels. The overall analysis indicates that the individuals who contributed to the mentioned samples are related, conversely to what is expected from a DNA Polymorphism Discovery Resource.

Although the presence of related samples might seem irrelevant for the study of autosomal polymorphisms in a given population, the study of the Y chromosome is limited by its haploidy and its low effective size. When studying the Y chromosome characteristics in Hg Q-M3, and considering the small number of individual belonging to this haplogroup together with the inclusion of paternally related samples, the conclusions driven by this analysis strongly tend to be erroneous. The results obtained from the analysis of the panels containing the mentioned samples (M90PDR and MPDR450) are biased by the inclusion of related males in the studied population, in addition to the low number of Hg Q-M3 samples. In particular, the conclusions driven by Repping et al. (2006) were based on the analysis of deleted samples with unknown spermatogenic status from each of the branches of the Y chromosome, indicating the structural variation among the haplogroups. Nevertheless, the analysis was neither supported by spermatogenic phenotype nor by the fertility status. Therefore, the association of Hg Q-M3 with the b2/b3 deletion is likely to be consequence of the bias produced by the incorrect selection criteria of the samples included in the DNA Polymorphism

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Discovery Resource, and not to a constitutive or characteristic deletion found in Hg Q-M3.

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.ygeno.2015.02.004.

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