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EDITORIAL

The Y chromosome and its fragility

After its discovery (Painter, 1921), the Y chromosome was viewed for a long period of time as a 'genetic wasteland' finalized only for testis determination. However, in 1976, two Italian geneticists proposed the existence of genes involved in spermatogenesis on the long arm of the Y chromosome (Yq) in the so called 'Azoospermia Factor' region (AZF) (Tiepolo & Zuffardi, 1976). After molecular tools became available, the predicted genes with specific male functions began to be identified such as the gene SRY encoding the testis-determining factor (Sinclair *et al.*, 1990) followed by candidate spermatogenetic genes located in the AZF regions (Skaletsky *et al.*, 2003). While the Y chromosome remained relatively unappealing for medical geneticists, it started gaining much attention from population geneticists and andrologists.

In fact, the discovery of AZF deletions represented a milestone in clinical andrology (Vogt *et al.*, 1996). Yq microdeletions are the most frequent known molecular genetic causes of azoo/severe oligozoospermia. Deletion frequency varies in different subgroups of patients according to sperm number (higher in azoospermic in respect to oligospermic men) and aetiology (higher in idiopathic than in non-idiopathic infertility). The analysis of normospermic controls, instead of fertile controls with unknown sperm count (a majority of studies used the later group of controls), allowed establishing a clear cut cause–effect relationship between AZF deletions and impaired sperm production (Krausz *et al.*, 2003). Moreover, studies with accurate genotype and phenotype description were able to establish the prognostic value of this genetic test i.e. to demonstrate that the type of deletion predicts the probability of testicular sperm retrieval in azoospermic men. Another important clinical correlate of Yq microdeletions is that they will be obligatorily transmitted to the male offspring and consequently, genetic counselling of couples prior to assisted reproduction is strongly recommended (for review, see Krausz & Degl'Innocenti, 2006).

While our knowledge on the clinical significance of Yq deletions has progressed, still very little is known about the AZF gene products. As deletions occur in block, removing more than one gene, the role of single AZF genes cannot be extrapolated from the AZF deletion phenotype and thus it is unclear if they are all participating in spermatogenesis. The deletion phenotypes suggest that the AZFa and AZFb regions contain at least one gene with essential spermatogenic function, whereas genes of the AZFc region are more likely to affect the efficiency of spermatogenesis. The incidence of AZF gene-specific deletions is clearly extremely low (<0.1%) and to date, only three confirmed gene specific deletions have been reported in the literature and are all in the same gene, USP9Y. In the current issue, Vogt *et al.* (2008) review recent acquisitions on AZF proteins and their potential functional contribution to human spermatogenesis.

New exciting areas of research in the Y chromosome field are partial AZFc deletions and duplications, both reported as risk factors for reduced sperm count. Among them, the so called gr/gr deletions are the most relevant (Repping *et al.*, 2003). Unfortunately, similar to the early AZF deletion studies, data in the literature are confusing and a meta-analysis is clearly impossible because of a number of biases (for review, see Krausz & Giachini, 2007). Given that the question is whether gr/gr deletions affect spermatogenesis and not sperm fertilizing ability, controls should be normozoospermia men. Despite this obvious concept, a majority of studies are based on 'fertile' control groups which, by definition, contain about 10% of severe and an even higher percentage of moderate/mild oligospermic individuals. Another important selection bias is the lack of ethnic and geographical matching of patients and controls. In the current issue, Tyler-Smith (2008) explains that comparisons between infertile and control groups in search of genetic susceptibility factors are more complex for the Y chromosome than for the rest of the genome because of population stratification and thus require unusual levels of confirmation. He also points out that population differences may exist in gr/gr deletion frequency and certainly more data with ethnically and geographically matched cases and controls are needed. However, if we consider only those studies in which all potential methodological and selection biases were avoided, gr/gr deletions are significant risk factors for impaired sperm production. In contrast to classical AZFc deletions, which are specific for spermatogenic failure, gr/gr deletions can be found also in normospermic men, although at a significantly lower frequency than in oligospermic patients. The relatively mild penetrance explains also its diffusion in the general population and the frequent father-to-son transmission. As gr/gr deletion is a transmissible risk factor (around 3–4% in oligospermic men), its screening can be proposed prior to assisted reproductive techniques. Although it is difficult

to predict the exact phenotype of the offspring, given that the father will transmit his entire Y chromosome with all potential factors capable of influencing the testicular phenotype, it is likely that his future son will have a similar impairment of the spermatogenesis.

As already mentioned, in the current issue, we have the pleasure to read two mini reviews by outstanding Y chromosome experts, P. H. Vogt and C. Tyler-Smith. They both highlight the peculiar structural organization and the presence of spermatogenic genes on the Y and how these factors may explain its convoluted history of deleterious, compensatory and advantageous rearrangements/mutations. It is also clear that this chromosome is susceptible to selection according to the phenotypic consequences of deletions on reproductive fitness and can no longer be considered a neutral locus.

The data presented in the two reviews and discussed during the Florence-Utah meeting clearly predict that this chromosome will remain among the favourites of all those who are interested in evolution, mutation mechanisms and reproductive biology.

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