NEWS AND COMMENTARY

The male-specific chromosome Y

Viewing the male-specific chromosome Y in a new light

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Several complex disorders (including autoimmune, inflammatory and cardiovascular diseases) display a strong sex bias that cannot be explained solely on the basis of differences in sex hormone production.¹ While it then becomes logical to consider the potential contributions of sex chromosomes, the latter have long constituted sort of a 'blind spot' in genetic association studies. For reasons that include lack of coverage, difficulties in genotype calling and the fact that chromosome X is not fully inactivated in females, the vast majority of genome-wide association studies (GWAS) have either not analyzed chromosome X properly or (most frequently) ignored it altogether. New computational methods are beginning to emerge to overcome these shortcomings.^{2,3} The situation is even more complicated for the male-specific portion of chromosome Y (MSY). Because MSY is transmitted in its entirety from father to son, polymorphisms on this chromosome are not useful in linkage-disequilibrium-based studies. One additional hurdle might in fact have been a 'cultural one': because of MSY losing most of its genes in the course of evolution, it has often been considered a 'degenerative' chromosome and a 'genetic wasteland' that plays no role beyond testis determination and sperm production,¹ and therefore not worthy of attention.

The review by Maan *et al.* provides us with a timely update of the progress made in recent years, along with additional structural and experimental insights. One turning point may have been the recent report that the genes escaping degeneration on MSY collectively represent a functional group that is critical for survival.⁴ The majority of these genes are dose-sensitive regulators that have an X-paralog that escapes X-inactivation, and their ubiquitous pattern of expression indicates that they may play other roles beyond reproductive functions. These genes are also predicted to be involved in cellular functions as basic as chromatin modification, ubiquitination, transcription, RNA splicing and translation. Such roles may explain findings from previous mouse studies where MSY variants are associated with either differences in gene expression and/or chromatin modifications in non-reproductive tissues.^{5,6} Studies on loss of chromosome Y have provided other functional insights, as they have shown that loss of chromosome Y is associated with higher cancer risk,⁷ and that some MSY genes (including those postulated to function as epigenetic regulators) may function as tumor suppressors.⁸ The authors also review the evidence implicating MSY genes in immune and/or inflammatory manifestations, the latter requiring coordination between many cell types whose functions may collectively be affected by changes in basic cellular functions.

Nonetheless, as the structure and putative functions of MSY genes are very similar to those of their X-paralogs, it is unclear whether the regulatory impact of MSY variants derives from either dose-related differences in the combined expression of X/Y paralogs, or functions related more specifically to MSY genes. Moreover, while various

studies have linked differences in the expression of some MSY genes to particular phenotypes, the full impact of such differences on corresponding proteins is not known. For instance, although the MSY DDX3Y gene is widely transcribed, it appears that its mRNA transcript might not be translated in all tissues.⁹ Beyond protein-coding genes, Maan *et al.* also remind us that MSY harbors genes that produce long and short non-coding RNAs that all have regulatory potential, but whose role has yet not been explored.

Sequencing of MSY has enabled the discovery of many SNPs on MSY, which has made it possible to construct a detailed phylogenetic tree of MSY lineages. These data have shown that human males can be divided into several haplogroups (ie, sets of humans that share a particular collection of MSY variants).¹⁰ In addition to phylogenetic studies, this system also makes it possible to test whether the prevalence or severity of disease traits differs among males according to their MSY haplogroups. The authors have pioneered such studies for cardiovascular phenotypes. One possible limitation to this approach may be that in most human populations (including Western Europe, Africa and Southern Asia) there is very little diversity in MSY haplotypes, with one single haplotype being greatly predominant in each population.¹⁰ In contrast, haplotypic MSY diversity is greater and better balanced in Eastern and/or Central Asia populations.¹⁰ Such populations might thus provide more power to MSY genetic investigations. Interestingly, Lu *et al.*¹¹ have recently found within a Han Chinese population that one particular MSY haplotype was more frequent in controls than in individuals with non-obstructive azoospermia. Moreover, they tested and confirmed that the corresponding MSY haplogroup showed significant interactions with autosomal SNPs found in previous GWAS to be associated with non-obstructive azoospermia. This approach could be extended to other phenotypes to reinvestigate existing GWAS, in particular those where male-specific associations have been found.

The findings reviewed by Maan *et al.* should serve as a motivation to improve our understanding of the biology and genetics of MSY genes. While this may provide some explanations for why some diseases are more frequent in males, such studies should be beneficial for female biology as well. Indeed, if one understands why MSY genes protect males against particular diseases, the findings could be used to design protective strategies in females. Finally, studies on MSY

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genes may also be helpful to better understand the biology of their paralogs on chromosome X.

CONFLICT OF INTEREST

The author declares no conflict of interest.

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