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Exploring the involvement of the regulatory genome in personalised medicine, drug response and disease stratification

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Human health is critically reliant, not only on the expression of normal proteins, but the appropriate expression of these proteins within the correct cells, in the correct amount and in response to the correct stimuli. However, very little is known about the components within the human genome that modulate normal gene expression or how they are compromised by polymorphic variation (SNPs) to increase disease susceptibility or alter drug response within the human population. Considering that the majority (87%) of disease associated SNPs identified by genome wide association studies are found outside of coding sequences, this lack of knowledge is hampering our ability to understand the genomic basis of disease and drug response stratification. Non-coding sequences called cis-regulatory sequences (CRSs) direct cell-specific and inducible gene expression in response to specific signal transduction networks. It is becoming apparent that many cases of disease susceptibility and drug response stratification are due to polymorphisms that alter CRS responses in a context-dependent manner. My seminar will describe the successful use of bioinformatics, cell based and transgenic methods used in our laboratory for identifying CRSs and analyzing the effects of disease associated allelic variation on their cell specificity and response to drug treatments. The technologies described build on the successes of ENCODE by exploring the effects of polymorphisms on CRS context dependency and drug response. This understanding is essential to uncovering the genomic basis of disease susceptibility and only by better understanding the effects of SNPs on the regulatory genome can we deliver on the promises of personalized medicine.

Biography

MacKenzie (AM) graduated with his Ph.D. from the University of Manchester in 1992 before carrying out 10 year of post-doctoral study at the University of Edinburgh. In 2001 AM set up his research lab at the University of Aberdeen and was promoted to Reader in 2008. He has published in many high impact journals such as *PNAS Mol. Psychiatry, J. Clin. Investigation, Arthritis and Rheumatism, Am. J. Psychiatry Neuropsychopharmacology* and most recently in *Biological Psychiatry* and *Trends in Molecular Medicine.*

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