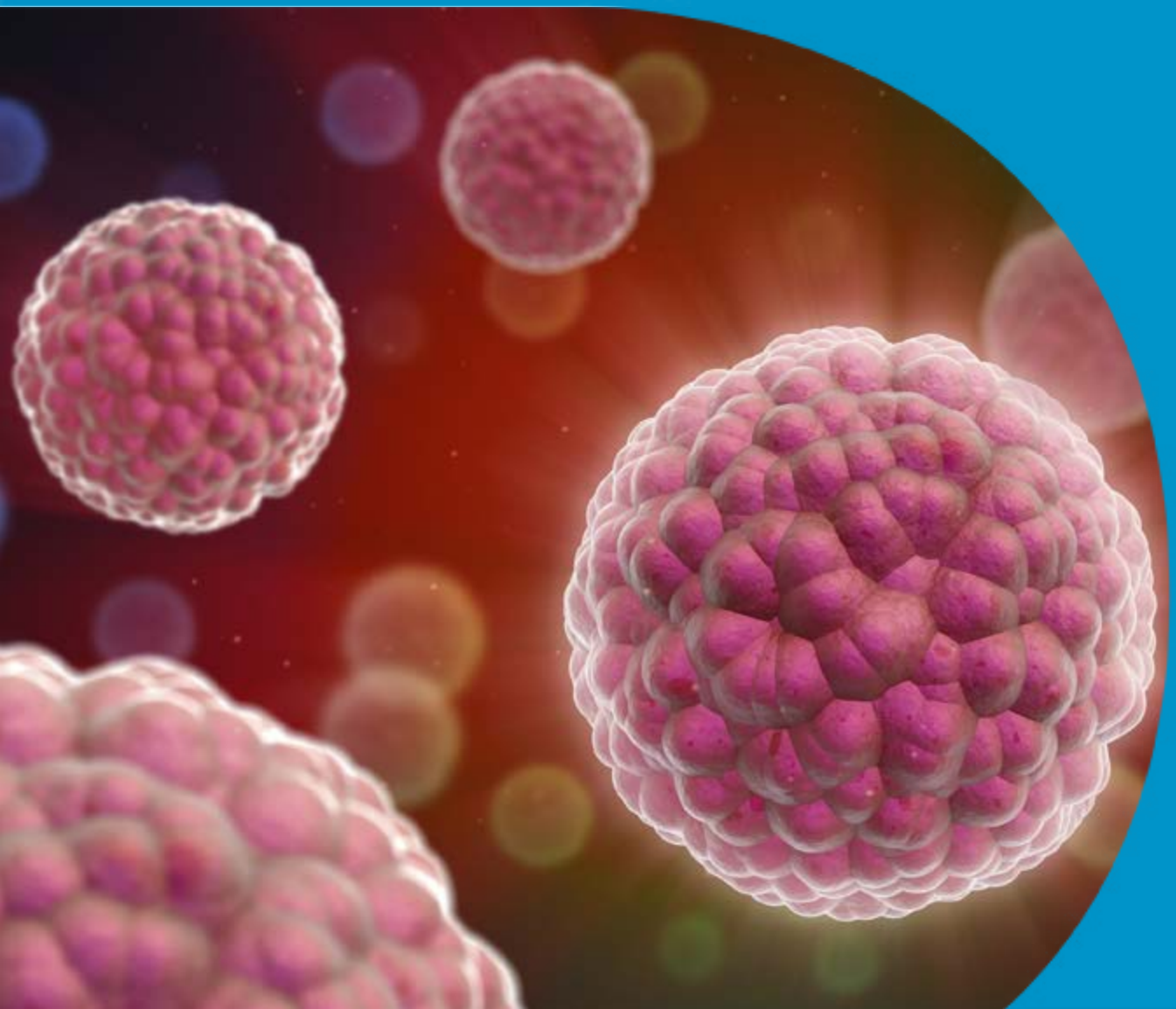
High Impact Paper of the Month
January 2015

Single Nucleotide Polymorphisms within Interferon Signaling Pathway Genes Are Associated with Colorectal Cancer Susceptibility and Survival.

Lu, S., Pardini, B., Cheng, B., Naccarati, A., Huhn, S., Vymetalkova, V., ... & Försti, A., 2014. *PloS one*, 9(10), e111061



Paper commentary

34 carefully selected SNPs, with potential links to colorectal cancer (CRC) risk and clinical outcome were analysed in 1327 CRC cases and 758 healthy controls in this blinded, hospital-based, case-control study. The 34 SNPs assayed were potentially functional genetic variants within Interferon signalling pathway genes. Genotyping was performed using KASP on an ABI real-time PCR machine, which delivered >99% accuracy and 97.0 – 99.5% call rate. As a result 7 SNPs associated with CRC susceptibility and two SNPs associated with CRC survival were identified.

Highlights of the paper

- Study conducted by a large consortium of high-profile research groups from Germany (DKFZ), Italy (Hu-GeF), Sweden and the Czech Republic.
- Application of KASP genotyping in a blinded, hospital-based, case-control study
- KASP genotyping used with >99% accuracy and concordance with duplicate sample quality controls.
- Genotype call rate range between 97.0 – 99.5%
- Example of KASP genotyping used to confirm positive association between patient genetic variation and CRC risk and survivability.
- KASP genotyping performed on whole genome amplified DNA performed on the ABI PRISM 7900HT sequence detection system.

Commentary

A large number of sequence variants are known to be associated with type 2 diabetes. Many common variants only confer modest to small effects on risk; the initial phase of this study was designed specifically to target low frequency SNPs with significant effects.
Initially, the whole genome sequencing which involved 2,630 Icelandic participants was combined with additional Icelandic cases and controls and further independent samples to boost the association data. This method successfully identified four new rare SNP variants that affect type 2 diabetes risk.

The large replication study that has followed confirms that carriers of low frequency G allele at rs76895963 are at approximately half the risk of type 2 diabetes compared to non-carriers. The rare G allele is associated with lower fasting glucose levels and higher insulinogenic index suggesting an effect on insulin secretion.
Genetic associations with human diseases need replicating and validating in independent studies to rule out false positives and to establish an unbiased effect size. Confirming a genetic association with a disease is a significant step towards understanding the underlying physiological mechanisms, diagnosis options, disease prediction and drug therapy targets. This study is just one of many studies worldwide which illustrate that following SNP discovery, KASP genotyping is the ideal choice for robust and successful replication and validation studies worldwide.

Other articles you may be interested in

Identification of low-frequency and rare sequence variants associated with elevated or reduced risk of type 2 diabetes.
Steinthorsdottir, V., Thorleifsson, G., Sulem, P., Helgason, H., Grarup, N., Sigurdsson, A., ... & Stefansson, K. (2014). Nature genetics, 46(3), 294-298.

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