

Using NGS Data to Detect Post-Zygotic Mutations in MZ twins

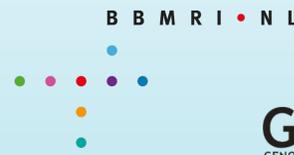
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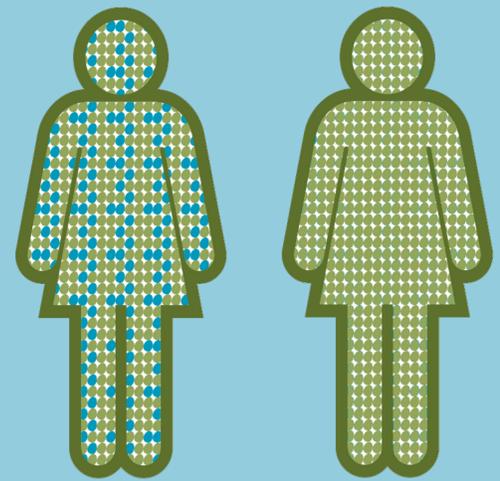
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Introduction

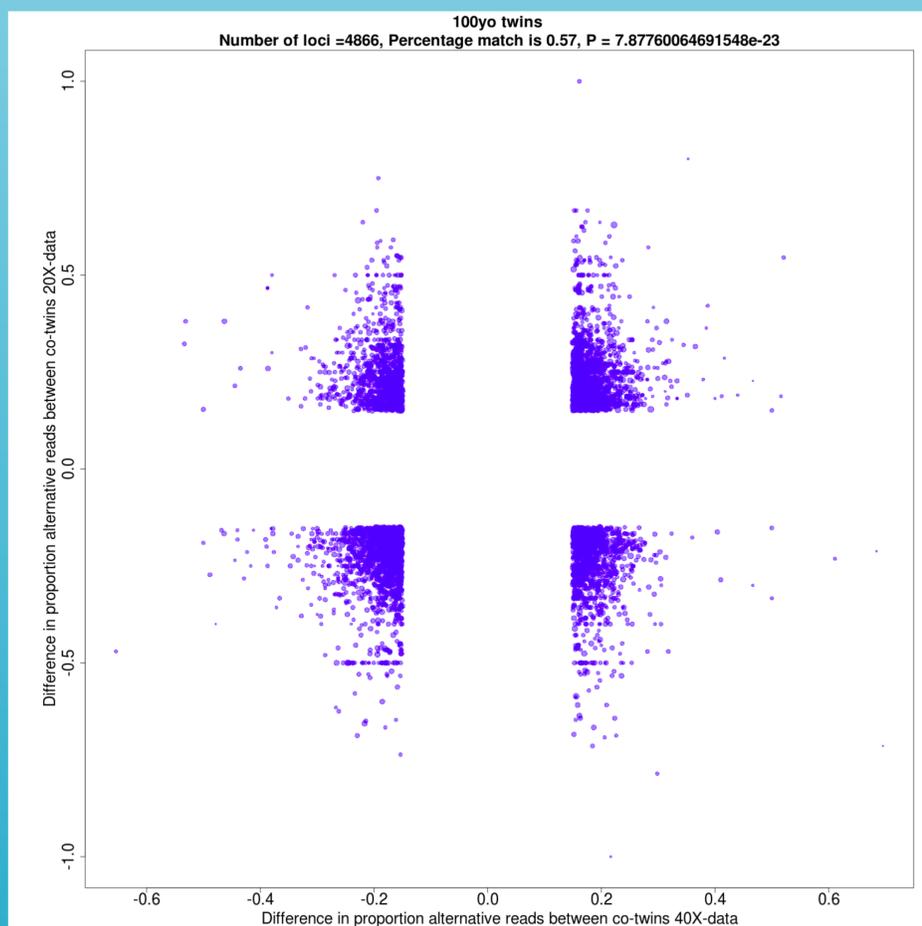
Monozygotic twins are often called *identical twins*, since they are presumed to have no differences at the level of DNA sequence. While monozygotic twins arise from one fertilized oocyte, there is a chance of mutation at each subsequent mitosis. The moment in life at which these mutations occur determines whether they are present in both twins, in only one twin, or in only a fraction of the cells in one twin.

Theories suggest somatic mosaicism is widespread and a very strong factor in determining the variability in disease risk between individuals¹. Mosaicism has been observed in several Mendelian diseases, for example in Alport Syndrome, where somatic mosaicism results in an unusually mild phenotype².



Data & Methods

We analyze DNA sequence data of two monozygotic twin pairs, 40 and 100 years old, for the presence of post-zygotic mutations, using differences in allele ratios as determinant for detection. Samples were sequenced twice on Illumina platforms (20X and 40X read depth) and were combined for increased specificity. Since the number of somatic mutations is related to age, and methylation data can be used as an indicator of biological age³, we can investigate the relation between the two. Lastly, we select sites from our resulting list of putative somatic mutations, and analyze RNA-sequence data to see if any of these sites contribute to variation in gene expression, (i.e. if the site is an eQTL). We then test for differential gene expression between co-twins to confirm the existence of the postzygotic mutations.



References

- 1 Frank, S. A. (2014). Somatic mosaicism and disease. *Current Biology*, 24(12), R577-R581.
- 2 Krol, R. P., Nozu, K., Nakanishi, K., Iijima, K., Takeshima, Y., Fu, X. J., ... & Yoshikawa, N. (2008). Somatic mosaicism for a mutation of the COL4A5 gene is a cause of mild phenotype male Alport syndrome. *Nephrology Dialysis Transplantation*, 23(8), 2525-2530.
- 3 Horvath, S. (2013). DNA methylation age of human tissues and cell types. *Genome biology*, 14(10), 1.