*i*SEQ lunch seminar series

Wednesday 14 October 2015 at 12.00 – 13.00

Kaitlin Samocha
Broad Institute of MIT and Harvard

Talk:
Using large reference-population call-sets to prioritize found variation in autism patients.

Abstract:
It is a primary challenge of human genetics to distinguish disease-causing rare variation from the multitude of more benign, low-frequency variants found in any genome. As a complement to methods that predict the deleteriousness of individual variants, we target variants found in genes that show unusually low levels of variation in healthy populations. Leveraging the large number of reference individuals in the call-set released by the Exome Aggregation Consortium (ExAC; n=60,706), our model of mutation predicts the number of expected rare (minor allele frequency <0.001) variants for each gene and identifies genes that are significantly depleted of loss-of-function and/or missense variation. Further, the vast number of observable rare variants in ExAC allows us the statistical power to use our method to search for missense-constrained regions within genes.

We applied both gene-level and region-level metrics of mutation intolerance (constraint) to *de novo* variants found in patients with autism spectrum disorders (ASDs; n=3,982) and controls (n=2,078). The previously established excess *de novo* loss-of-function variation found in ASD manifests primarily in genes we identify as highly loss-of-function constrained. We also find that the regions with the most severe missense constraint have a higher rate of *de novo* missense variants found in cases when compared to the rate seen in controls. By contrast, those regions under no constraint show no difference between case and control *de novo* rates. These analyses highlight the use of evaluating genic intolerance to mutations when interpreting the variation found in patients.

Venue:
Merete Barker Auditory, The Lakeside Theatres, Aarhus University, Bartholins Allé 3, 8000 Aarhus C.

Refreshments:
Sandwiches will be provided. Therefore, please email Anne Hedemand (anne@biomed.au.dk) no later than 12 October 2015, if you would like to participate.

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