Année de publication : 2015

Grimm D.G., Azencott C.A., Aicheler F., Gieraths U., MacArthur D.G., Samocha K.E., Cooper D.N., Stenson P.D., Daly M.J., Smoller J.W., thers (2015 Jan 1)

The evaluation of tools used to predict the impact of missense variants is hindered by two types of circularity

Human mutation : 36 : 513-523

Résumé

Année de publication : 2014

Cendrine Tourette, Francesca Farina, Rafael P Vazquez-Manrique, Anne-Marie Orfila, Jessica Voisin, Sonia Hernandez, Nicolas Offner, J Alex Parker, Sophie Menet, Jinho Kim, Jungmok Lyu, Si Ho Choi, Kerry Cormier, Christina K Edgerly, Olivia L Bordiuk, Karen Smith, Anne Louise, Michael Halford, Steven Stacker, Jean-Philippe Vert, Robert J Ferrante, Wange Lu, Christian Neri (2014 Jun 25)

The Wnt receptor Ryk reduces neuronal and cell survival capacity by repressing FOXO activity during the early phases of mutant huntingtin pathogenicity.

PLoS biology : e1001895 : DOI : 10.1371/journal.pbio.1001895

Résumé

The Wnt receptor Ryk is an evolutionary-conserved protein important during neuronal differentiation through several mechanisms, including γ-secretase cleavage and nuclear translocation of its intracellular domain (Ryk-ICD). Although the Wnt pathway may be neuroprotective, the role of Ryk in neurodegenerative disease remains unknown. We found that Ryk is up-regulated in neurons expressing mutant huntingtin (HTT) in several models of Huntington's disease (HD). Further investigation in Caenorhabditis elegans and mouse striatal cell models of HD provided a model in which the early-stage increase of Ryk promotes neuronal dysfunction by repressing the neuroprotective activity of the longevity-promoting factor FOXO through a noncanonical mechanism that implicates the Ryk-ICD fragment and its binding to the FOXO co-factor β-catenin. The Ryk-ICD fragment suppressed neuroprotection by lin-18/Ryk loss-of-function in expanded-polyQ nematodes, repressed FOXO transcriptional activity, and abolished β-catenin protection of mutant htt striatal cells against cell death vulnerability. Additionally, Ryk-ICD was increased in the nucleus of mutant htt cells, and reducing γ-secretase PS1 levels compensated for the cytotoxicity of full-length Ryk in these cells. These findings reveal that the Ryk-ICD pathway may impair FOXO protective activity in mutant polyglutamine neurons, suggesting that neurons are unable to efficiently maintain function and resist disease from the earliest phases of the pathogenic process in HD.

Nelle Varoquaux, Ferhat Ay, William Stafford Noble, Jean-Philippe Vert (2014 Jun 17)

A statistical approach for inferring the 3D structure of the genome.
Bioinformatics (Oxford, England) : i26-33 : DOI : 10.1093/bioinformatics/btu268

Résumé

Recent technological advances allow the measurement, in a single Hi-C experiment, of the frequencies of physical contacts among pairs of genomic loci at a genome-wide scale. The next challenge is to infer, from the resulting DNA-DNA contact maps, accurate 3D models of how chromosomes fold and fit into the nucleus. Many existing inference methods rely on multidimensional scaling (MDS), in which the pairwise distances of the inferred model are optimized to resemble pairwise distances derived directly from the contact counts. These approaches, however, often optimize a heuristic objective function and require strong assumptions about the biophysics of DNA to transform interaction frequencies to spatial distance, and thereby may lead to incorrect structure reconstruction.

Elsa Bernard, Laurent Jacob, Julien Mairal, Jean-Philippe Vert (2014 May 9)
Efficient RNA isoform identification and quantification from RNA-Seq data with network flows.
Bioinformatics (Oxford, England) : 2447-55 : DOI : 10.1093/bioinformatics/btu317

Résumé

Several state-of-the-art methods for isoform identification and quantification are based on [Formula: see text]-regularized regression, such as the Lasso. However, explicitly listing the-possibly exponentially-large set of candidate transcripts is intractable for genes with many exons. For this reason, existing approaches using the [Formula: see text]-penalty are either restricted to genes with few exons or only run the regression algorithm on a small set of preselected isoforms.

Ferhat Ay, Evelien M Bunnik, Nelle Varoquaux, Sebastiaan M Bol, Jacques Prudhomme, Jean-Philippe Vert, William Stafford Noble, Karine G Le Roch (2014 Mar 26)
Three-dimensional modeling of the P. falciparum genome during the erythrocytic cycle reveals a strong connection between genome architecture and gene expression.
Genome research : 974-88 : DOI : 10.1101/gr.169417.113

Résumé

The development of the human malaria parasite Plasmodium falciparum is controlled by coordinated changes in gene expression throughout its complex life cycle, but the corresponding regulatory mechanisms are incompletely understood. To study the relationship between genome architecture and gene regulation in Plasmodium, we assayed the genome architecture of P. falciparum at three time points during its erythrocytic (asexual) cycle. Using chromosome conformation capture coupled with next-generation

sequencing technology (Hi-C), we obtained high-resolution chromosomal contact maps, which we then used to construct a consensus three-dimensional genome structure for each time point. We observed strong clustering of centromeres, telomeres, ribosomal DNA, and virulence genes, resulting in a complex architecture that cannot be explained by a simple volume exclusion model. Internal virulence gene clusters exhibit domain-like structures in contact maps, suggesting that they play an important role in the genome architecture. Midway during the erythrocytic cycle, at the highly transcriptionally active trophozoite stage, the genome adopts a more open chromatin structure with increased chromosomal intermingling. In addition, we observed reduced expression of genes located in spatial proximity to the repressive subtelomeric center, and colocalization of distinct groups of parasite-specific genes with coordinated expression profiles. Overall, our results are indicative of a strong association between the P. falciparum spatial genome organization and gene expression. Understanding the molecular processes involved in genome conformation dynamics could contribute to the discovery of novel antimalarial strategies.

Année de publication : 2013

Veronika Graml, Xenia Studera, Jonathan L D Lawson, Anatole Chessel, Marco Geymonat, Miriam Bortfeld-Miller, Thomas Walter, Laura Wagstaff, Eugenia Piddini, Rafael E Carazo-Salas (2013 Nov 2)

A genomic Multiprocess survey of machineries that control and link cell shape, microtubule organization, and cell-cycle progression.

Developmental cell : 227-39 : DOI : 10.1016/j.devcel.2014.09.005

Résumé

Understanding cells as integrated systems requires that we systematically decipher how single genes affect multiple biological processes and how processes are functionally linked. Here, we used multiprocess phenotypic profiling, combining high-resolution 3D confocal microscopy and multiparametric image analysis, to simultaneously survey the fission yeast genome with respect to three key cellular processes: cell shape, microtubule organization, and cell-cycle progression. We identify, validate, and functionally annotate 262 genes controlling specific aspects of those processes. Of these, 62% had not been linked to these processes before and 35% are implicated in multiple processes. Importantly, we identify a conserved role for DNA-damage responses in controlling microtubule stability. In addition, we investigate how the processes are functionally linked. We show unexpectedly that disruption of cell-cycle progression does not necessarily affect cell size control and that distinct aspects of cell shape regulate microtubules and vice versa, identifying important systems-level links across these processes.

James C Costello, Laura M Heiser, Elisabeth Georgii, Mehmet Gönen, Michael P Menden, Nicholas J Wang, Mukesh Bansal, Muhammad Ammad-ud-din, Petteri Hintsanen, Suleiman A Khan, John-Patrick Mpindi, Olli Kallioniemi, Antti Honkela, Tero Aittokallio, Krister Wennerberg, , James J

Collins, Dan Gallahan, Dinah Singer, Julio Saez-Rodriguez, Samuel Kaski, Joe W Gray, Gustavo Stolovitzky (2013 Jul 20)

A community effort to assess and improve drug sensitivity prediction algorithms.

Nature biotechnology : 1202-12 : DOI : 10.1038/nbt.2877

Résumé

Predicting the best treatment strategy from genomic information is a core goal of precision medicine. Here we focus on predicting drug response based on a cohort of genomic, epigenomic and proteomic profiling data sets measured in human breast cancer cell lines. Through a collaborative effort between the National Cancer Institute (NCI) and the Dialogue on Reverse Engineering Assessment and Methods (DREAM) project, we analyzed a total of 44 drug sensitivity prediction algorithms. The top-performing approaches modeled nonlinear relationships and incorporated biological pathway information. We found that gene expression microarrays consistently provided the best predictive power of the individual profiling data sets; however, performance was increased by including multiple, independent data sets. We discuss the innovations underlying the top-performing methodology, Bayesian multitask MKL, and we provide detailed descriptions of all methods. This study establishes benchmarks for drug sensitivity prediction and identifies approaches that can be leveraged for the development of new methods.

Rosa M Suárez, Franciane Chevot, Andrea Cavagnino, Nicolas Saettel, François Radvanyi, Sandrine Piguel, Isabelle Bernard-Pierrot, Véronique Stoven, Michel Legraverend (2013 Mar 1)

Inhibitors of the TAM subfamily of tyrosine kinases: synthesis and biological evaluation.

European journal of medicinal chemistry : 2-25 : DOI : 10.1016/j.ejmech.2012.06.005

Résumé

The TAM subfamily of Receptor Tyrosine Kinases (RTKs) contains three human proteins of therapeutical interest, Axl, Mer, and Tyro3. Our goal was to design a type II inhibitor specific for this family, i.e. able to interact with the allosteric pocket and with the hinge region of the kinase. We report the synthesis of several series of purine analogues of BMS-777607. The structural diversity of the designed inhibitors was expected to modify the interactions formed in the binding site and consequently to modulate their selectivity profiles. The most potent inhibitor **6g** exhibits K_ds of 39, 42, 65 and 200 nM against Axl, Mer, Met and Tyro3 respectively. Analysis of the affinity of **6g** for active and inactive forms of Abl1, an RTK protein that does not belong to the TAM subfamily, together with the binding modes of **6g** predicted by docking studies, indicates that **6g** displays some selectivity for the TAM family and may act as a type II inhibitor.

Année de publication : 2012

Claude Houdayer, Virginie Caux-Moncoutier, Sophie Krieger, Michel Barrois, Françoise Bonnet, Violaine Bourdon, Myriam Bronner, Monique Buisson, Florence Coulet, Pascaline Gaildrat, Cédrick Lefol, Mélanie Léone, Sylvie Mazoyer, Danielle Muller, Audrey Remenieras, Françoise Révillion, Etienne Rouleau, Joanna Sokolowska, Jean-Philippe Vert, Rosette Lidereau, Florent Soubrier, Hagay Sobol, Nicolas Sevenet, Brigitte Bressac-de Paillerets, Agnès Hardouin, Mario Tosi, Olga M Sinilnikova, Dominique Stoppa-Lyonnet (2012 Apr 17)

Guidelines for splicing analysis in molecular diagnosis derived from a set of 327 combined in silico/in vitro studies on BRCA1 and BRCA2 variants.

Human mutation : 1228-38 : DOI : 10.1002/humu.22101

Résumé

Assessing the impact of variants of unknown significance (VUS) on splicing is a key issue in molecular diagnosis. This impact can be predicted by in silico tools, but proper evaluation and user guidelines are lacking. To fill this gap, we embarked upon the largest BRCA1 and BRCA2 splice study to date by testing 272 VUSs (327 analyses) within the BRCA splice network of Unicancer. All these VUSs were analyzed by using six tools (splice site prediction by neural network, splice site finder (SSF), MaxEntScan (MES), ESE finder, relative enhancer and silencer classification by unanimous enrichment, and human splicing finder) and the predictions obtained were compared with transcript analysis results. Combining MES and SSF gave 96% sensitivity and 83% specificity for VUSs occurring in the vicinity of consensus splice sites, that is, the surrounding 11 and 14 bases for the 5′ and 3′ sites, respectively. This study was also an opportunity to define guidelines for transcript analysis along with a tentative classification of splice variants. The guidelines drawn from this large series should be useful for the whole community, particularly in the context of growing sequencing capacities that require robust pipelines for variant interpretation.

Année de publication : 2009

Mikhail Zaslavskiy, Francis Bach, Jean-Philippe Vert (2009 May 30)

Global alignment of protein-protein interaction networks by graph matching methods.

Bioinformatics (Oxford, England) : i259-67 : DOI : 10.1093/bioinformatics/btp196

Résumé

Aligning protein-protein interaction (PPI) networks of different species has drawn a considerable interest recently. This problem is important to investigate evolutionary conserved pathways or protein complexes across species, and to help in the identification of functional orthologs through the detection of conserved interactions. It is, however, a difficult combinatorial problem, for which only heuristic methods have been proposed so far.

Année de publication : 2008

Laurent Jacob, Jean-Philippe Vert (2008 Aug 5)

Protein-ligand interaction prediction: an improved chemogenomics approach.

Bioinformatics (Oxford, England) : 2149-56 : DOI : 10.1093/bioinformatics/btn409

Résumé

Predicting interactions between small molecules and proteins is a crucial step to decipher many biological processes, and plays a critical role in drug discovery. When no detailed 3D structure of the protein target is available, ligand-based virtual screening allows the construction of predictive models by learning to discriminate known ligands from non-ligands. However, the accuracy of ligand-based models quickly degrades when the number of known ligands decreases, and in particular the approach is not applicable for orphan receptors with no known ligand.

Année de publication : 2006

K Kruse, J F Joanny, F Jülicher, J Prost (2006 Jul 11)

Contractility and retrograde flow in lamellipodium motion.

Physical biology : 130-7

Résumé

We present a phenomenological description of cell locomotion on a solid substrate. The material properties of the actin cytoskeleton in the lamellipodium are described by the constitutive equations of a viscous polar gel with intrinsic activity. The polymerization of the gel takes place in a localized region near the leading edge. Using a simple two-dimensional description, we calculate in the steady state the thickness profile of the lamellipodium which at the rear connects to the cell body; we also calculate the flow profiles and the forces exerted on the substrate. The cell velocity is estimated as a function of externally applied forces. Our description is consistent with experimentally observed properties of motile cells such as the existence of a retrograde flow in the lamellipodium and a dipolar force distribution exerted by the cell on the substrate.