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CONFERENCIAS PLENARIAS

"A SESENTA AÑOS DE LA PRIMERA IMAGEN DE LA MOLÉCULA DE LA VIDA"

CONFERENCIA INAUGURAL "Dr. Francisco Sáez". Sociedad Argentina de Genética
EN BUSCA DE LA INTERACCIÓN GENÉTICO – AMBIENTAL

Picardi LA. Cátedra de Genética – Facultad Ciencias Agrarias – Campo Villarino – CIUNR - Universidad Nacional de Rosario.
e-mail: lpicardi@unr.edu.ar

Desde el nacimiento de la Genética Cuantitativa en el siglo pasado la partición de la variancia fenotípica observable en un carácter es un cuasi dogma. De él aprendimos que esta variación es debida al aporte de los genes que lo rigen más el efecto del ambiente y que al aplicar variancia surge la covariación de genes con ambiente. Esto implica que para un carácter en la población siempre existe esta interacción: un ruido que debemos reducir. Aceptamos que este componente genético puede particionarse en componentes aditivos, dominantes y epistáticos. Los genetistas cuantitativos somos afectos a estimar la heredabilidad de los caracteres debida a la variación de los efectos aditivos y nos convencemos que así tenemos controlado el ruido ambiental para tomar decisiones en planes de mejora. También podemos segregar efectos maternos en cruzamientos, que son parte de la variancia ambiental y dilucidar, cuando diseñamos experimentos de selección a largo plazo, que recombinaciones intra bloques génicos liberan nueva variancia aditiva. Podemos hasta discutir el paradigmático caso de nula heredabilidad de la fertilidad femenina que desde los tiempos de Sir Ronald Fisher se considera agotada por ser un carácter de adaptación y selección exhaustiva en la evolución de la especie. Como todo es finito, y en ciencia los dogmas no deberían existir, éstos se modifican rápidamente. Las herramientas moleculares nos brindaron la oportunidad de identificar genes, ver sus efectos en el fenotipo y ya sin tanto ruido tratamos ahora de capturar QTLs (*Quantitative Traits Loci*). Ríos de tinta corren ahora para saber cuánto de la variación del carácter es explicada por los QTLs que señalan los marcadores moleculares. Nuevamente queremos saber como los afectaría el ambiente, tanto el correspondiente al contexto genético en que se detectan como el ambiente en que se expresan. Podemos así seguir entretenidos con estimaciones de la interacción genético–ambiental. Ahora tenemos que agregar un nuevo ruido. Sabemos un poco más sobre el *imprinting*, nueva propiedad de los genes. Según ella, la dominancia o recesividad depende de si el gen es aportado por el padre o la madre. Hasta ahora esto ha sido estudiado en los genes mayores pero no podemos ignorar que esté presente, aunque no lo detectemos, en la variación de genes que tienen efectos menores sobre el fenotipo. Últimamente para mayor intranquilidad también debemos releer a Lamarck. Sus teorías han sido puestas bajo el área de la epigenética, que investiga cambios heredables en la expresión de los genes sin modificación en el ADN. Estos cambios se producen por influencia del ambiente donde se desarrolla el genotipo. Distintos experimentos sugieren que ¨marcas¨ epigenéticas establecidas durante la vida del organismo pueden pasar a las siguientes generaciones. Por lo tanto la partición de la variancia fenotípica cobra ahora otra dimensión. Estas nuevas propiedades de los genes pertenecen a la variancia genética o a la ambiental? Desde la primera imagen que nos diera Rosalind Franklin nos hemos separado en caminos altamente disciplinares alejándonos del mundo de la integración. Quizás ahora sea el momento de transitar este camino.

CELL-CELL COMMUNICATION DURING FERTILIZATION IN *Arabidopsis thaliana*

Kessler SA, H Lindner, L Müller, A Boisson-Dernier, H Shimosato-Asano, U Grossniklaus. Institute of Plant Biology & Zürich-Basel Plant Science Center, University of Zürich, Zollikerstrasse 107, 8008 Zürich, Switzerland.
e-mail: grossnik@botinst.uzh.ch

Research in our laboratory centers on the developmental genetics of plant reproduction, focusing on cell specification during gametogenesis and on cellular interactions during double fertilization. After deposition of the pollen on the stigma, it germinates, grows through style and transmitting tract, and finally enters the micropyle of the ovule, attracted by a chemotactic signal produced by the female gametophyte (Okuda *et al*., 2009). The final step is the reception of the pollen tube by one of the synergid cells that flank the egg cell, followed by the cessation of pollen tube growth and its subsequent rupture to release the sperm cells. We have isolated and characterized female gametophytic mutants that disrupt pollen tube reception. Pollen tubes that encounter such mutant female gametophytes are unable to rupture and release the sperm cells to effect double fertilization (Huck *et al*., 2003; Kessler *et al*., 2010). These phenotypes suggest that the female gametophyte controls the behaviour of the male gametophyte (pollen) in this process. One of the mutants, *feronia,*

was shown to affect a receptor-like kinase (Escobar-Restrepo *et al*., 2007), while another, *nortia*, disrupts a seven-transmembrane-domain-protein similar to the powdery mildew resistance protein Mlo (Kessler *et al*., 2010). Our recent studies of this pathway have revealed surprising links to disease resistance in plants, the evolutionary implications of which are intriguing. Forward and reverse genetic approaches have identified various novel factors involved in this communication process, which is essential to plant reproduction. Importantly, it appears that pollen tube reception also provides a barrier to inter-specific hybridization. We have recently identified components that are specific to this function at the molecular level. I will report on the characterization of the components in this signal transduction cascade.

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Huck N, Moore JM, Federer M, Grossniklaus U (2003) The Arabidopsis mutant feronia disrupts the female gametophytic control of pollen tube reception. Development 130:2149-2159

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Okuda S, Tsutsui H, Shiina K, Sprunck S, Takeuchi H, Yui R, Kasahara RD, Hamamura Y, Mizukami A, Susaki D, Kawano N, Sakakibara T, Namiki S, Itoh K, Otsuka K, Matsuzaki M, Nozaki H, Kuroiwa T, Nakano A, Kanaoka MM, Dresselhaus T, Sasaki N, Higashiyama T (2009) Defensin-like polypeptide LUREs are pollen tube attractants secreted from synergid cells. Nature 458:357-361

GENOMIC SELECTION TO IMPROVE PRODUCTION FROM LIVESTOCK AND CROPS

Hayes BJ[1,2,3]. [1]Biosciences Research Division, Department of Primary Industries, Bundoora, Victoria 3083, Australia. [2]Dairy Futures Cooperative Research Centre, Victoria 3083, Australia. [3]La Trobe University, Bundoora, Victoria 3086, Australia.
e-mail: Ben.hayes@dpi.vic.gov.au

Increasing food production to meet demand given projected population growth is a major challenge for the coming decades. A new technology called genomic selection is likely to play a role in breeding more efficient and higher yielding livestock and crops to meet this demand. The motivation for genomic selection has been the results from genome wide association studies in livestock, and humans. Results from these studies have led to the conclusion that the effect of individual quantitative trait loci (QTL) on complex traits, such as yield, are likely to be small, and that a large number of QTL are necessary to explain the genetic variation in these traits. Genomic selection overcomes this problem by estimating breeding values as the sum of the effect of all of the dense DNA markers across the genome. In dairy cattle breeding particularly, the accuracy of genomic estimated breeding values which can be achieved, combined with the fact that these are available early in life has lead to rapid adoption of the technology. Genomic selection allows for increased rates of gain for traits which have been hard to select for in the past, for example feed conversion efficiency. In order to successfully apply genomic selection to a wider range of livestock and crops, it is important to understand the parameters which determine the accuracy of genomic predictions. The accuracy of genomic predictions can be shown to be dependant on the size of the reference population in which the DNA marker effects are estimated, the heritability of the trait, the number of loci affecting the trait, or the effective population size, and the proportion of genetic variance captured by the markers. Statistical methodology also plays a role, particularly the agreement between the assumed distribution of QTL effects and the true distribution. By comparing deterministic predictions of the accuracy of genomic selection, and those observed in real livestock populations, insights can be gained into the requirements for a successful genomic selection program. Finally, the application of new technologies, such as whole genome sequencing, to further accelerate gains from genomic selection is discussed.

GENOME PREDICTION OF GENETIC VALUES IN PLANTS USING LINEAR AND NON-LINEAR MODELS

Crossa J[1], G de los Campos[2], P Perez[3]. [1]Biometrics and Statistics Unit, International Maize and Wheat Improvement Center (CIMMYT), Apdo. Postal 6-641, 06600, México DF, México. [2]Department of Biostatistics, University of Alabama at Birmingham, Ryals Public Health Bldg 443, Alabama, USA. [3]Colegio de Postgraduados, Montecillo, Edo. de México, México.
e-mail: J.CROSSA@cgiar.org

The availability of high density panels of molecular markers has prompted the adoption of genomic

selection (GS) methods in animal and plant breeding. In GS, parametric, semi-parametric regressions, and non-parametric methods are used. Interactions between marker alleles at two or more loci can be accommodated in a linear model by using appropriate contrasts. However, this is feasible only when the number of markers (p) is moderate. In GS, however, p is usually large, making parametric modeling of complex epistatic interactions unfeasible. An alternative is to use semi-parametric regressions and non-parametric methods, such as kernel-based methods with the expectation that such procedures can capture complex higher order interaction patterns. In this presentation we show how to use kernel methods for prediction with dense molecular markers. We illustrate the use of linear and non-linear on simulated data and on real maize line genotyped with 55k markers and evaluated for several trait-environment combinations. We also show results from wheat multi trait multi environments trials. The empirical results indicated that the models have similar prediction accuracy, with slight superiority of the kernel models over the linear model. Non-linear models may be capturing epistatic effects and showed slight and consistent prediction accuracy superiority over the linear model.

MUTATION, DRIFT, AND THE ORIGIN OF SUBCELLULAR FEATURES

Lynch M. Department of Biology, Indiana University, Bloomington, USA.
e-mail: milynch@indiana.edu

Understanding the mechanisms of evolution and the degree to which phylogenetic generalities exist requires information on the rate at which mutations arise and their effects at the molecular and phenotypic levels. Although procuring such data has been technically challenging, high-throughput genomic sequencing is rapidly expanding our knowledge in this area. Most notably, information on spontaneous mutations, now available in a wide variety of organisms, implies an inverse scaling of the mutation rate (per nucleotide site) with the effective population size of a lineage. The argument will be made that this pattern naturally arises as natural selection pushes the mutation rate down to a lower limit set by the power of random genetic drift rather than by intrinsic molecular limitations on repair mechanisms. Additional support for this idea derives from the relative levels of efficiency of DNA polymerases and mismatch-repair enzymes in eukaryotes relative to prokaryotes. This drift-barrier hypothesis has general implications for all aspects of evolution, including the performance of enzymes and the stability of proteins. The fundamental assumption is that as molecular adaptations become more and more refined, the room for subsequent improvement becomes diminishingly small. If this hypothesis is correct, the population-genetic environment imposes a fundamental constraint on the level of perfection that can be achieved by any molecular adaptation. It also implies that effective neutrality is the expected outcome of natural selection, an idea first suggested by Hartl et al. in 1985. Although generally viewed as an independent process, mutation also operates as a weak selective force, thereby playing a central role in "nearly neutral" hypotheses in evolution. Most notably, genes and proteins with more complex structures are subject to higher rates of mutational degeneration simply because they are larger mutational targets. However, because the mutation rate is very low at the nucleotide level, the efficiency of such mutation-associated selection becomes of diminishing significance in populations with small effective sizes. Thus, mutationally hazardous genomic and gene-structural features, which may or may not be adaptive, are expected to passively arise in lineages with small effective sizes. This general principle, the mutational-hazard theory, will be illustrated with examples including: 1) the differential expansion of intron numbers in various phylogenetic lineages; and 2) the diversification of protein-architectural features.

EMBELLECIMIENTO, FALSIFICACIÓN Y FRAUDE EN CIENCIA. PÉRDIDA DE LA INOCENCIA

Bianchi NO. IMBICE, 1900 La Plata, Argentina.
e-mail: nobianchi@speedy.com.ar

La investigación científica requiere del mecenazgo de alguna entidad que aporte financiación. Sin embargo los fondos destinados a la creación científica son siempre insuficientes para subsidiar todos los buenos proyectos presentados, lo cual genera una competencia habitualmente encarnizada entre los postulantes. La obtención de un subsidio depende del prestigio del grupo de investigación, de la originalidad del proyecto y de la existencia de resultados y publicaciones que avalen la posibilidad de cumplir con el plan propuesto. La necesidad de

"*vender*" un proyecto para obtener la financiación del mismo puede conducir a conductas impropias que varían desde una mera transgresión a la veracidad, hasta una deshonestidad que corroe el prestigio del mendaz o que incluso es legalmente punible. El "*embellecimiento*", el "*síndrome palimpséstico*", la "*criptomnesia*", el "*plagio*", la "*falsificación*" y el "*fraude*" son formas distintas y crecientes de deshonestidad científica que serán definidas e ilustradas mediante ejemplos de la literatura. Varias publicaciones han cuantificado la frecuencia de la malversación científica. La frecuencia es baja (0.02%) cuando se la estima por el descubrimiento y castigo del malversante. Opuestamente, llega a cifras ~70% cuando la estimación se hace por la confesión de los que han incurrido directa o indirectamente en alguna transgresión. Esto demuestra que la mayor parte de las conductas inapropiadas no son descubiertas ni penadas, pese a que no son excepciones a la regla, sino la regla con excepciones. En 1942, el sociólogo Logan Wilson empleó por primera vez la frase "*Publish or perish*" ("publicar o perecer"). Desde entonces el "publicar o perecer" se emplea rutinariamente por los científicos para enfatizar que la vida profesional de un investigador depende en gran medida del número de trabajos que consiga publicar ya que estos son la certificación de su idoneidad profesional. Se comentaran las distintas formas de corruptelas en las publicaciones científicas y se hará especial mención de la "*autoría ficticia ("ghostwriting")*, la cual es una de las formas más comunes de deshonestidad en la publicación. Es casi una norma que cuando se descubre una deshonestidad científica por denuncias de uno o más investigadores, no solamente se afecta la carrera y el prestigio del transgresor sino también la de los denunciantes. Se aportaran casos paradigmáticos de la literatura que avalan esta aseveración. La "conferencia Favret" será el resumen de un ensayo redactado con formato de libro, y de autoría del conferencista. Los interesados en leer el texto completo del ensayo podrán solicitarlo enviando el siguiente mensaje: "*solicito el texto completo de la Conferencia Favret*" a la dirección de correo electrónico que figura en el encabezado, o alternativamente a nobianchi_2000@yahoo.com.

GENOMICS IN MATERNAL AND CHILD HEALTH: FUTURE POSSIBILITIES

Guttmacher AE, M.D. Director, Eunice Kennedy Shriver National Institute of Child Health and Human Development, National Institutes of Health
e-mail: NICHDDirectorsOffice@mail.nih.gov

Sixty years after the first image of the molecule of life we are now at the brink of molecular medicine. New tools and scientific insights are creating unique opportunities to translate research findings into novel prevention strategies and therapies, and into optimal practice. This presentation explores what that translation might look like in the areas of maternal and child health. The application of such new tools as genome sequencing and genome-wide association studies and of such developing tools as epigenomics and genome-based newborn screening should dramatically improve our understanding of health and disease and change health care globally.

CONFERENCIA "Danko Brncic". Sociedad de Genética de Chile
THE GENETICS OF BIODIVERSIFICATION: LESSONS FROM THE CACTOPHILIC *Drosophila*

Markow TA. Division of Biological Sciences. University of California at San Diego. USA.
e-mail: tmarkow@ucsd.edu

Species of the genus *Drosophila* number approximately 3,000, and they range in their ecologies from human commensals to specialists on chemically diverse hosts such as mushrooms or cacti. Among the species whose ecologies are best characterized are the cactophilic *Drosophila* species found in North and South America. I will describe the radiations of these species, their unique host associations, and the genetics underlying their ability to utilize these resources. As a group, the cactophilic *Drosophila* are highly speciose, presenting a continuum of different stages of the evolution of reproductive isolation. Thus they offer an unprecedented model system to study the genetics of speciation.

CONFERENCIA DE CIERRE ALAG/2012
SCIENCE IN LATIN AMERICA AND ELSEWHERE: FOUR DECADES OF PLEASURES AND CONCERNS

Salzano FM. Departamento de Genética, Instituto de Biociências, Universidade Federal do Rio Grande do Sul, Caixa Postal 15053, 91501-970 Porto Alegre, RS, Brazil

e-mail: francisco.salzano@ufrgs.br

The Latin American Association of Genetics (ALAG) was founded in July 3, 1969, in Porto Alegre, and in the ensuing 43 years organized 15 congresses in nine countries of the region. Although in these meetings the different areas of genetics were represented in different proportions, they could be regarded as representing well the science cultivated in the continent. This period was characterized by an explosive world science development, with a most productive union between genetics, molecular biology, bioinformatics, and nanotechnology. Investigation of the genetic structure of living and extinct organisms, and its application in medicine, agriculture, and animal science, yielded an enormous amount of data, most of it freely available to scientists of developed and underdeveloped countries. The internet opened new possibilities of instant contact with the information as it is made available, and laboratory methods of analysis are becoming cheaper. For those who regard knowledge acquisition as a most pleasing challenge the present situation can be considered as exceptionally favorable. But the economic situation in Latin America remains unstable, and governments are not considering science development a priority. It is the task of the present generation to try to change this panorama, since it is only through science that we can achieve better ways of living in a socially more equitable world.

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