ACCADEMIA NAZIONALE DEI LINCEI

Conference

LA GENETICA A 200 ANNI DALLA NASCITA DI MENDEL: PASSATO, PRESENTE E FUTURO

6-7 DICEMBRE 2022

A B S T R A C T

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PROGRAMME

Gregor Mendel, con i suoi esperimenti sui piselli, elucidò i meccanismi di trasmissione delle caratteristiche ereditarie, spiegando come e perché alcuni caratteri dei genitori si trasmettano ai figli e con ciò pose le basi della genetica, scienza che oggi ha un ruolo centrale nelle scienze della vita. Essa, infatti, cerca di comprendere cosa determini la nostra identità e quella di tutti i viventi, uno dei problemi che hanno sempre affascinato l'uomo. Quando la genetica nacque, nel 1866, in realtà l'ambizione era forse minore, in quanto si cercava, partendo dalla semplice osservazione delle somiglianze fra genitori e figli, di spiegare quali meccanismi potessero giustificare il fatto che alcune delle nostre caratteristiche venissero ereditate di generazione in generazione. C'è voluto parecchio tempo per capire che il segreto della identità dei viventi, e quindi anche della nostra di esseri umani, è scritto in una molecola chiamata DNA ed in particolare in una più o meno lunga stringa di caratteri con un alfabeto costituito da sole 4 lettere, A, C, G e T. Ci vorrà ancora del tempo per capire come esattamente quella lunga stringa dalla struttura così semplice riesca a determinare ciò che noi siamo. Nel 2022 cade il bicentenario della nascita di Mendel e ci sembra opportuno proporre un'iniziativa in cui, oltre a ripercorrere la storia della genetica, si guardi a ciò che si è fatto fino ad ora e a ciò che presumibilmente si può fare in termini di avanzamento delle conoscenze e di applicazioni pratiche.

Martedì 6 dicembre

10.00 Roberto ANTONELLI (Presidente dell'Accademia Nazionale dei Lincei): *Indirizzi di saluto*

Session 1: Chair: Michele MORGANTE

10.10 Telmo PIEVANI (Università degli Studi di Padova): *Genetics and Mendel: an historical perspective*

10.40 Thomas KUNKEL (National Institutes of Health, Research Triangle Park, North Carolina, USA): *The importance of model organisms*

11.10 Pausa caffè

11.30 Detlef WEIGEL (Max Planck Institute for Biology Tübingen): *Paranoid Plants: When Too Much Genetic Diversity Is Harmful*

12.00 Mariano ROCCHI (Università degli Studi di Bari): *Chromosome evolution*

12.30 Giuseppe MACINO (Linceo, Sapienza Università di Roma): *Epigenetics*

13.00 Intervallo

Session 2: Chair: Antonella RUSSO

15.00 Cedric FESCHOTTE (Cornell Cals, Ithaca, Ny, USA): *Transposable elements as catalysts of genome evolution*

15.30 Mario VENTURA (Università degli Studi di Bari): *The journey through the human genome sequencing: what we have learned*

16.00 Guido BARBUJANI (Università degli Studi di Ferrara): *Population genetics and genomics*

16.30 Pausa caffè

16.50 Orsetta ZUFFARDI (Università degli Studi di Pavia): *Mutations and diseases*

17.20 Luis HERRERA ESTRELLA (Cinvestav UGA-LANGEBIO, Messico): *Present, past and future of genetic modifications in plants*

17.50 Luigi NALDINI (Linceo, Università Vita-Salute San Raffaele di Milano): *Genetic modifications in humans*

Mercoledì 7 dicembre

Session 3: Presiede: Edgardo FILIPPONE

9.00 Marco BAZZICALUPO (Università degli Studi di Firenze): *Microorganisms genetics*

9.30 Luigi CATTIVELLI (CREA - Fiorenzuola d'Arda): *Mendelian genetic, i.e. the use of mutations to revolutionize agriculture*

10.00 Roberto TUBEROSA (Università di Bologna): *Mendelizing quantitative traits*

10.30 Pausa caffè

10.50 Lucio LUZZATTO (Linceo, Università di Firenze, Muhimbili University, Dar-es-Salaam, Tanzania): *Mendelian genetics in the human species*

11.20 Francesco SALAMINI (Linceo, Università di Colonia, Germania): Conclusions

Il convegno è organizzato in collaborazione con l'Associazione Genetica Italiana (AGI), la Società Italiana di Genetica Agraria (SIGA) e la Società Italiana di Mutagenesi Ambientale e Genomica (SIMAG)

ROMA - PALAZZO CORSINI - VIA DELLA LUNGARA, 10
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Nel rispetto delle limitazioni imposte per l'emergenza Covid-19, il numero dei posti in sala sarà limitato (vedi: https://www.lincei.it/it/news/misure-fronteggiare-lemergenza-epidemiologica).
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I lavori potranno essere seguiti dal pubblico anche in streaming
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The importance of model organisms

Thomas KUNKEL (National Institutes of Health, Research Triangle Park, North Carolina, USA)

In celebration of the birth of Gregor Mendel and 70 years after the initial description of the structure of DNA, much is now known about how DNA is replicated accurately and how inaccuracy leads to mutations that shape evolution and the formation of human diseases. Some of this information comes from studies of replication in 'model' organisms. This includes my group's own work in budding yeast. These studies reveal that the fidelity of replication of undamaged eukaryotic nuclear DNA is primarily determined by (1) the nucleotide selectivity of three major replicases, DNA polymerases α, δ and ε, (2) the ability of DNA polymerases δ and ε to proofread mismatches made during replication, and the ability of (3) DNA mismatch repair and (4) ribonucleotide excision repair to remove newly incorporated mismatches and ribonucleotides following replication. Here I briefly consider how these four processes work in series to achieve enormously accurate DNA replication, and how mutator phenotypes incurred by inactivating one or more of these fidelity steps may promote evolution and initiate human disease.

Paranoid Plants: When Too Much Genetic Diversity Is Harmful

Detlef WEIGEL (Max Planck Institute for Biology Tübingen)

My group is addressing fundamental questions in evolutionary biology, using both genome-first and phenotype-first approaches. A few years ago, we discovered that Arabidopsis thaliana is a great model for the study of hybrid necrosis. This widespread syndrome of hybrid failure in plants is caused by plant paranoia – regardless of the presence of enemies, plants "think" they are being attacked by pathogens. The consequence is autoimmunity, which can be extreme enough to kill plants before they set seeds. Over the past decade, we have studied in detail the underlying genetics, finding that often only one or two loci are involved, with most of them encoding NLR immune receptors. The NLR gene family is the most variable gene family in plants, and it is thus not surprising that they are often involved in genome-genome conflict, with alleles at one locus greatly changing the activity of alleles at another locus. Similarly, we have found that autoimmunity due to allelic variation at the ACD6 locus, which probably encodes a channel, is modulated by a slew of extragenic suppressors. I will describe what we have learned and how our unique angle on studying the plant immune system has led to insights that were not obtained with conventional laboratory genetics. Additional information about our work can be found on our website http://weigelworld.org.

Chromosome evolution

Mariano ROCCHI (Università degli Studi di Bari)

Various tools can be used to trace the evolutionary history of living species. These include paleontology, comparative anatomy, and ancient DNA sequencing. Cytogenetics is yet another tool; it can be used to study the chromosomal changes that different species have undergone during evolution. As chromosomal preparations can be made only from dividing cells, the only way to track the evolution of chromosomes is to compare them in closely related living species. For humans, this means comparing human chromosomes, in order of proximity, first with those of chimpanzees, gorillas and orangutans, and then with those of Old and New World monkeys.

The first example of how our evolutionary history is written on our chromosomes is the fusion of two ancestral chromosomes that gave rise to human chromosome 2. Other examples concern a phenomenon whereby the centromere has moved to a different position on the chromosome. Several of these examples have been documented in the evolution of primates. Presumably the repositioning of the centromere, by inactivating the old one and seeding a new one in a different position, occurs relatively frequently, but only a few of these become fixed in the population over time. To determine the frequency of such events one needs to screen large populations. Prenatal testing for chromosomal abnormalities in humans can be viewed as a large population study of normal individuals. Examples of repositioned centromeres found in these studies will be discussed.
Evolution is still a controversial issue. For this reason, chromosomes are very suitable for teaching evolution as they are directly visible to the human eye and do not require calculations to interpret the findings.

Epigenetics

Giuseppe MACINO (Linceo, Sapienza Università di Roma)

Organisms are required to adjust to environmental fluctuations, and selective forces appear to act on environmentally induced modifications in development, a process suggested to be essential for adaptive speciation. Epigenetic marks such as DNA methylation, histone modifications, and the generation of regulatory small non-coding RNA molecules, represent an efficient means to modulate gene activity in response to internal and external stimuli. The highly dynamic nature of epigenetic adjustments suggests their involvement in heritable adaptive responses via transmission of epigenetic marks from one generation to the next, independently of DNA sequence changes. An altered epigenetic status can be stably inherited but alternatively, might also exhibit metastable characteristics and will revert after a variable number of replication rounds. Yet, once acquired, epigenetic adjustments can be highly stable even on an evolutionary scale.

The journey through the human genome sequencing: what we have learned

Mario VENTURA (Università degli Studi di Bari)

Almost twenty-one years ago, the first "draft" of the human genome was generated and has been continually improved over the past decade (GRCh38/hg38). Despite its scientific and economic impact, the human reference genome was incomplete with multiple gaps and misassemblies and comprised mosaics of many haplotypes, thus highlighting the need to produce a new complete reference genome. Using a haploid CHM13 cell line and new sequencing technologies, the T2T consortium has generated a new human genome assembly that provides access to centromeric and ribosomal sequences, and the full repertoire of euchromatic segmental duplications (SDs), three types of sequences underrepresented or totally unresolved in the GRCh38.
This new assembly is an exciting advance and an important step to i) understand the biology of centromeric function and epigenetic signature in the human genome and ii) deeply characterize the sequence and variability over the p-arm of the acrocentric human chromosomes and iii) assemble and study genes in SDs. Overall, this will better support personalized medicine, population genomic analysis, and genome editing. Furthermore, the continued joint effort between the T2T Consortium and the Human Pangenome Reference Consortium, aiming to produce high-quality assemblies from diverse human populations,

will provide additional protocols for routinely assemble diploid genomes to represent all possible alternative sequences observed across different haplotypes

Present, past and future of genetic modifications in plants

Luis HERRERA ESTRELLA (Cinvestav UGA-LANGEBIO, Messico)

At the beginning of the 20th century a bacterium was identified as the causal agent of the crown-gall disease. This bacterium called Agrobacterium tumefaciens causes the formation of tumors in the stems of plants causing great losses for agriculture, particularly affecting fruit tree yield. After several decades of research, it was discovered that A. tumefaciens induced tumor formation by transferring a segment of bacterial DNA into the chromosomes of plant cells. The transferred DNA encodes genes involved in the production of phytohormones that promote the disorganized growth of plant cells causing tumor formation. In the 1980s the bacterial plasmid responsible for tumor formation was altered to enable the transfer of target genes into plant cells without affected cell growth, leading to the development of the technology to produce transgenic plants. Few years after the development of plant gene transfer technology several applications were developed to create plants resistant to pests and viral diseases. Soon, private enterprises acquired the intellectual property behind the technology to produce transgenic plants and several commercial products were released into the market. Herbicide resistant and insect resistant transgenic crops were rapidly adopted by farmers and over 100 million hectares of transgenic crops are currently grown in several countries in the world. Although the technology had clear benefits for farmers and some applications like pest resistant crops lead a significant reduction in pesticide application, public perception on transgenic crops has turned increasingly negative. More recently gene editing using the CRISPR/Cas9 system has opened a whole new universe of possibilities for plant genetic engineering by introducing multiple beneficial alleles more rapidly and effectively into crops or even to create greater genetic diversity than that currently available in domesticated plants. Although gene editing produces changes like those naturally caused by mutation during the evolution of any organisms, it is still controversial whether gene edited crops can be considered as equal to conventional breeding or as transgenic plants. In this paper I will briefly review how the technology to produce transgenic plants was developed (particularly at European universities), their current and future applications, as well as the development of gene editing technology for plants, including fascinating new development to perform gene editing in the greenhouse without the need of tissue culture step, and its potential to accelerate plant breeding.

Genetic modifications in humans

Luigi NALDINI (Linceo, Università Vita-Salute San Raffaele di Milano)

Gene therapy aims to transfer new genetic information to directly treat a disease at its genetic roots, by replacing a malfunctioning gene within the tissue cells adversely affected by the condition, or instruct a novel function to improve cellular performance, as in the case of immune cells fighting against tumors. Gene transfer, however, must overcome several cellular and tissue barriers to effectively deliver new genetic information into the target cell nucleus and drive proficient expression of the therapeutic molecule without disrupting essential regulatory mechanism. The gene corrected cells must be in sufficient amount to reverse the pathological condition, escape immunological recognition and survive long-term or transmit their genetic modification to their progeny to sustain the

benefit. Early attempts at gene therapy conducted in the nineties reported several failures and some clinical success, however accompanied by the occurrence of severe adverse events in some treated individuals, raising concerns and skepticism over further deployment of these strategies. Yet, after nearly 20 years of work to improve gene transfer platforms, the last decade has seen a turning point for the gene and cell therapy field, with increasing numbers of patients showing remarkable and durable benefits from the treatments and a growing number of novel advanced medicines being developed for the treatment of genetic diseases and tumors reaching the market. In parallel, we have witnessed the emergence of a new generation of therapies based on gene editing technologies, which exploit so-called “molecular scalpels” (such as those derived from CRISPR/Cas) to cut a specific location in a target gene, inactivating or "rewriting" its sequence. These approaches open unprecedented therapeutic possibilities including precisely correcting in situ the mutations causing genetic diseases and enhancing the activity of immune cells against tumors. While these exciting developments provide the foundation of a novel personalized and precise molecular medicine, they also pose a set of new challenges to science as well as the whole society. The high costs of development and production may challenge the sustainability of these promising treatments by national health systems and/or health insurances and constrain fair and equitable access by patients. While current studies are carried out on somatic cells and therefore remain confined to the subject receiving the gene therapy treatment, editing technologies could possibly be applied to the germ line to prevent transmission of a mutant gene. This scenario calls for a scientific and ethical reflection to address the biosafety, social responsibility and moral lawfulness of introducing genetic modifications into the gene pool of our species

Microorganisms genetics

Marco BAZZICALUPO (Università degli Studi di Firenze)

Just as Mendel did not know microorganisms, they have long been almost ignored by geneticists well after the rediscovery of Mendel’s lows. From the 1950s on however, rooted in the Mendel’s legacy, microbial genetics became the driving force pushing tremendous advances in genetics: bacteria, phages and fungi contributed to fundamental insights in genetic topics such as mutation, recombination, genetic control of gene expression, gene conversion, mitochondrial and somatic genetics up to restriction enzymes and genetic engineering. Although from the 1980s on, most of the more astounding genetic discoveries were on higher organisms, with less clamor, genetic studies on microorganisms kept up the pace. Here some of the more exciting and promising research areas on microbial genetics will be presented: system biology and metabolic modeling, genetic manipulation, gene transfer and evolutionary mechanisms, the metagenome with community genetics and relations between genes and environment, and finally, our far remote past, the very beginning of life on earth

Mendelian genetic, i.e. the use of mutations to revolutionize agriculture

Luigi CATTIVELLI (CREA - Fiorenzuola d'Arda)

Le leggi di Mendel se da un lato hanno messo le basi per tutta la genetica moderna, dall’altro hanno anche posto l’attenzione sull’utilizzo delle mutazioni nel miglioramento genetico. Le mutazioni genetiche, naturali o indotte, sono alla base del plant breeding fin da quando il miglioramento genetico era un’attività totalmente empirica. La

domesticazione delle piante è determinata da un set di mutazioni spontanee note come domestication sindrom che sono selezionate dai primi agricoltori, allo stesso modo il lavoro di Nazareno Strampelli negli anni '20 e la green revolution degli anni '60 e '70 sono basti su poche mutazioni in geni capaci di influire in modo significativo sulla produttività delle piante. Oltre al carattere produzione, i mutanti hanno un grande ruolo nella definizione delle resistenze genetiche alle malattie (le resistenze sono quasi tutte di tipo qualitativo), nell'adattamento all'ambiente e persino in molti tratti che descrivono la qualità dei prodotti alimentari come il colore (e la conseguente presenza di composti pigmentati a valenza nutrizionale) o la forma di frutta e verdura.
Per tanti anni la genetica dei caratteri qualitativi è stata separata da quella dei caratteri quantitativi, e anche se la genomica moderna consente oggi di risolvere i caratteri qualitativi in singoli geni ed alleli con un piccolo effetto sul fenotipo, è indubbio che la genetica mendeliana basata su mutazioni in geni con forte impatto sul fenotipo ha rappresentato nell'ultimo secolo il principale motore del miglioramento genetico. Oggi, tecnologie del genome editing stanno rivoluzionando il miglioramento genetico agrario sottolineando ancora una volta il ruolo delle mutazioni e del loro impatto sul fenotipo.
A distanza di circa 150 anni dalle scoperte di Mendel, è evidente che la genetica "mendeliana", basata sull'uso di mutazioni in geni con un chiaro e misurabile impatto sul fenotipo, è stata e rimane la strada più efficace per selezionare le piante necessarie al sostentamento dell'uomo.

Mendelizing quantitative traits

Roberto TUBEROSA (Università di Bologna)

I caratteri quantitativi rappresentano buona parte della variabilità misurata nelle specie viventi. La loro complessa base genetica, anche in funzione del carattere in oggetto, è determinata da numerosi QTL (Quantitative Trait Loci), porzioni di DNA ciascuna delle quali è ereditata secondo le leggi di Mendel ed il cui effetto sul fenotipo è molto variabile a seconda del QTL coinvolto, motivo per cui l'identificazione (mappatura) ed il clonaggio di major QTL con rilevante effetto sul fenotipo sono di grande interesse per il miglioramento genetico delle colture agrarie, soprattutto nel caso dei cereali che forniscono, fino al 70% della calorie della dieta.
I recenti progressi della genomica e del sequenziamento dei genomi consentono di mappare meglio e clonare i major QTL, molto utili per applicare la selezione assistita con marcatori (MAS: Marker Assisted Selection) e ancje le TEA (Tecnologie di Evoluzione Assistita), ovvero l'editing dei geni, due tecnologie fondamentali per selezionare nuove varietà. La ricerca genomica delle piante e le TEA hanno dimostrato che non esiste un "muro di Berlino" tra la classica genetica Mendeliana e la genetica dei caratteri quantitativi e che le rispettive conoscenze si fondono e rafforzano nella "genomica circolare" (dal fenotipo al gene/QTL e viceversa), strategia fondamentale per migliorare al meglio la produttività e stabilità produttiva delle colture agrarie.
La relazione presenterà alcuni esempi in merito al ruolo ed al clonaggio di major QTL coincidenti con geni Mendeliani, anche nel caso delle "non coding sequences" (NCS), la parte prevalente (fino al 90% nei cereali) e meno conosciuta del genoma, porzione a suo tempo definita "junk DNA" (DNA spazzatura), causa la scarsa conoscenza sugli effetti sul fenotipo. Il miglioramento genetico moderno delle colture agrarie utilizza ampiamente la MAS ed utilizzerà sempre più l'editing di major QTL, definiti nel loro insieme come QTLome, cioè la punta dell'iceberg del genoma, la cui parte sommersa e prevalente è costituita da minor QTL non mappabili come tali, ma i cui effetti possono comunque essere utilizzati tramite la selezione genomica

Mendelian genetics in the human species

Lucio LUZZATTO (Linceo, Università di Firenze, Muhimbili University, Dar-es-Salaam, Tanzania)

It is gratifying for a haematologist that, when Mendel's laws were 're-discovered' at the beginning of the last century, this happened in part thanks to the development of blood transfusion, that required investigation of what became known as the ABO blood groups. This genetic system served to verify in the human species Mendel's work; at the same time, it helped to start refining it further. With reference to Mendel's first law, the ABO system immediately demonstrated that alleles for a certain character could be more than two, and that dominance was a relative concept (since A and B are co-dominant; and A2 is recessive with respect to A1, but dominant with respect to O). With reference to Mendel's second law, in all families investigated segregation seemed perfect (once A1 and A2 were understood). As for Mendel's third law, independent assortment was also verified, until inheritance of the nail-patella syndrome was investigated: this led to the discovery of the first autosomal linkage in humans.

Mendel's most important notion was that inheritance did not result from blending: rather, it is particulate, and therefore there must exist units of inheritance (the word gene had not yet been coined). Exporting Mendel's work to the human species was on one hand impossible, because crosses cannot be designed at the will of the investigator (and designs of this sort should be outlawed); on the other, compared to garden peas, human individuals can be and are often studied in greater detail: the formal study of inheritance in families came to be known as pedigree analysis, and the study of allele frequencies as populations genetics. Conceptual and technical advances have led to the development of biochemical genetics, and subsequently of molecular genetics: looking at the essence, it was all still Mendel. In the human species medicine bears witness to how cultural evolution has surpassed biological evolution; and medical genetics is still to a large extent Mendelian. This is best symbolized by the monumental effort spearheaded by Victor McKusick, Mendelian Inheritance in Man (MIM, now OMIM): this database, first created in 1966, now lists some 8000 diseases and 15,000 genes.

The very terms dominant and recessive denote that Mendel had a clear concept of what was genotype and what was phenotype. Today we recognize that whereas genotype at a particular locus is uniquely defined by the allelic genes there present, the phenotype, being the appearance of the genotype, depends on the means used in order to examine the appearance (clinical, biochemical, microscopic, tomographic, etc), and it also depends on influences from other genetic loci: thus, the genotype is an absolute entity, the phenotype is not. Similarly, the entire genome of an individual is an absolute – the inherited DNA sequence – but all other -omes are not: the epigenome, the transcriptome, the proteome vary from one cell to another, from one point in time to another, and they depend on the sensitivity of the methods used to analyse them.

Finally, sometimes the impression has been given that, in contrast to the notion of a Mendelian trait, the number and impact of modifier genes may be overwhelming; and when data on a large enough population are available, one may find that almost any gene in the genome has an effect (the omnigenic model). However, a haematologist can recognize sickle cell anaemia even when co-existing with □-thalassaemia or G6PD deficiency: we may call these modifiers or their effects epistatic, but HBBE6V remains a clinically recessive Mendelian gene. On Gregor Mendel's 200th birthday, we may well wish him well