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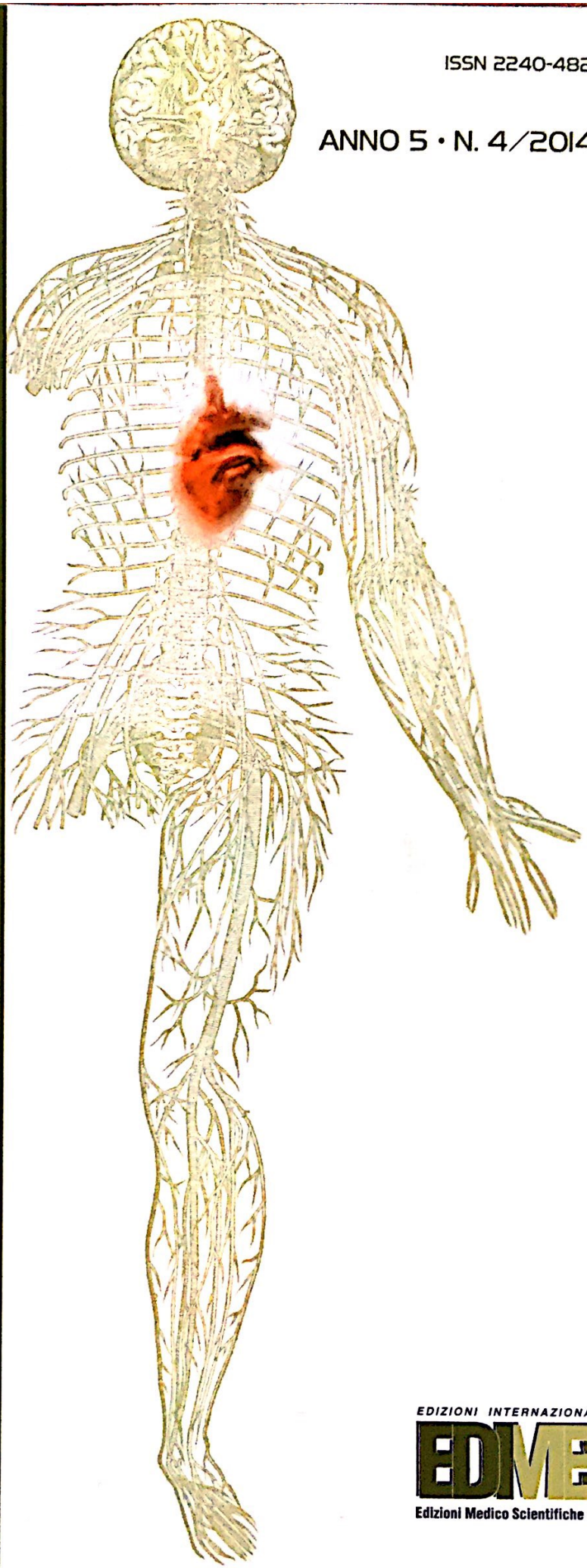

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NEXT GENERATION SEQUENCING: A NEW METHODOLOGICAL APPROACH FOR THE MOLECULAR DIAGNOSIS OF GENETIC DYSLIPIDEMIAS

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The high demand for low-cost sequencing has driven the development of high-throughput sequencing (or next-generation sequencing) technologies that parallelize the sequencing process, producing thousands or millions of sequences concurrently. Ion Torrent PGM System (Life Technologies) developed a system based on using standard sequencing chemistry, but with a novel, semiconductor based detection system. This method of sequencing is based on the detection of hydrogen ions that are released during the polymerization of DNA, as opposed to the optical methods used in other sequencing systems. Ion AmpliSeqDesigner is a free online tool that allows researchers to create and order Ion AmpliSeqDNA Custom Panels comprising human genes of interest. The Ion AmpliSeq workflow is based on a transformative technology that simplifies ultrahigh-multiplex PCR amplification and library construction and requires only 10 ng of input DNA per pool. We designed two different panels to analyze genes involved in primary hypercholesterolemia or hypocholesterolemia in order to perform molecular diagnosis in patients with definite clinical criteria. The laboratory workflow consist of the following steps: library construction, preparation of template, run of sequence, data analysis. We used three different chips (314, 316, 318) with a range of sequence reads from 400-550 thousand to 4-5.5 million. Bioinformatic analysis was conducted by The Ion Reporter System which is a combined hardware and software solution for analyzing human sequencing data. It consists of a locally deployed computer with a suite of informatics tools that streamlines and simplifies analysis, variant annotation, and archiving of semiconductor sequencing data. In this work we describe the workflow and output of this approach in subjects with primary hypercholesterolemia and primary hypocholesterolemia performed in our laboratory.

LIPOPROTEIN SUBFRACTIONS AND SUBCLINICAL ATHEROSCLEROSIS

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Plasma cholesterol is a well-established cardiovascular risk factor. The reduction of serum cholesterol and Low-Density-Lipoprotein Cholesterol (LDL-C) decreases the risk of cardiovascular disease. Nevertheless, even in subjects who reach their target LDL-C, a risk of morbidity and mortality for cardiovascular disease remains (residual risk). Other lipid factors, in addition to LDL-C, could be responsible for the residual risk.

Lipoprint® is a method based on the pre-staining of the lipid fractions in serum with Sudan black and subsequent electrophoresis in gradient polyacrylamide gel and measures the levels of esterified cholesterol in each class of lipoproteins. The carotid intima-media thickness (IMT), as assessed by B-mode ultrasonography, is a validated marker of subclinical atherosclerosis. The purpose of the present study was to assess the relationship between cholesterol content in VLDL, IDL, LDL, and HDL, measured by Lipoprint® and carotid IMT and plaques, in 228 post-menopausal Neapolitan women participating to ATENA project. VLDL-C had a positive correlation with carotid IMT ($r=0.26$, $p<0.001$).
This association was retained after adjustment for the main confounding factors ($r=0.45$, $p<0.04$). LDL-C and IDL-C had a statistically significant association with IMT, that was lost after adjustment for major confounding factors. HDL-C did not show any association with carotid IMT. In the second and third tertiles of VLDL-C the risk of common carotid plaques was doubled, compared to the first tertile (respectively OR 2.0, 95% CI 1.01-3.98, p=0.047 and OR 2.02 95% CI 1.05-3.90, p=0.034). Tertiles of VLDL-C + IDL-C (taken together) showed a significant association with carotid plaques, even after adjustment for age, systolic blood pressure, blood glucose, cigarette smoking, BMI and HDL-C. In conclusion, measurement of cholesterol concentration in different lipoprotein classes by Lipoprint® is a potentially useful tool for the quantification of cardiovascular risk.

EFFETTI DI BARNIDIPINA E PERINDOPRIL, IN MONOTERAPIA O IN COMBINAZIONE CON SIMVASTATINA, SULLA STEATOSI EPATICA ED I PARAMETRI METABOLICI IN PAZIENTI IPERTESI

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Obiettivo. Valutare gli effetti di barnidipina o perindopril in monoterapia o in combinazione con simvastatina su alcuni parametri metabolici e sul grado di steatosi epatica, in pazienti ipertesi con steatosi epatica non alcolica.
Materiali e Metodi. Sono stati arruolati 149 pazienti con ipertensione lieve-moderata (pressione sistolica ≥140 e <180 mmHg e pressione diastolica ≥90 e <105 mmHg), normocolesterolemici (LDL-C <160 mg/dl), in sovrappeso o obesi (BMI 25,0-34,9 kg/m^2) e con steatosi epatica. I pazienti sono stati randomizzati ad assumere barnidipina, 20 mg/die, o perindopril, 5 mg/die, per 6 mesi; successivamente simvastatina, 20 mg/die è stata aggiunta ad entrambi i trattamenti per ulteriori 6 mesi. I pazienti sono stati sottoposti ad un esame ecografico per valutare il grado di steatosi, definita con un punteggio da 0 a 3, il diametro del tessuto adiposo sottocutaneo e del tessuto adiposo viscerale e ad un prelievo di sangue per valutare la glicemia plasmatica a digiuno (FPG), l'insulinemia plasmatica a digiuno (FPI), il colesterolo totale (TC), i trigliceridi (Tg), il colesterolo HDL (HDL-C), il colesterolo LDL (LDL-C) e alcuni parametri infiammatori tra cui l'adiponectina (ADN), il fattore di necrosi tumorale-α (TNF-α), l'interleuchina-6 (IL-6), la proteina C reattiva ad alta sensibilità (Hs-CRP), al basale e dopo 6 e 12 mesi, rispettivamente. È stata, inoltre, misurata la pressione arteriosa ogni mese.

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