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Alla c.a.
Ministero della Salute
Direzione Generale della Ricerca
e dell'Innovazione in Sanità
Viale Giorgio Ribotta 5
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invio via Workflow

Trieste, *data della firma digitale*

Oggetto: Obiettivi e modalità di utilizzo del finanziamento relativo al 5 per mille anno 2010, 2011, 2012, 2013 e 2015.

Il finanziamento del 5 per mille - in coerenza con la legge 266/05 che prevede la possibilità per il contribuente di vincolare il 5 per mille della imposta sul reddito a sostegno della attività di ricerca sanitaria, e in ottemperanza a quanto comunicato dal Ministero in data 18.07.08 che precisa che tale contributo sia da considerarsi come aggiuntivo al finanziamento per la RC e quindi soggetto a programmazione e rendicontazione secondo le linee di ricerca in cui si articola l'attività dell'Istituto - consente di sviluppare ulteriormente programmi di ricerca già in atto, di attivarne di nuovi nell'ambito delle linee esistenti e di acquisire di conseguenza beni e servizi atti a realizzare tali progetti di ricerca con particolare riferimento, nel caso di questo I.R.C.C.S., a progetti a forte caratterizzazione traslazionale.

Relativamente all'utilizzo dei fondi del 5 per mille anno 2010, 2011, 2012, 2013 e 2015, comunicazioni Workflow ID 2013000246 dd.17/01/2013, ID 2014002517 dd. 07/05/2014 e ID 2015000426 dd.28/01/2015, valuta la rilevanza scientifica del progetto **"*Genetics of senses and related diseases*"**, è emersa la necessità di rimodulare le ripartizioni finanziarie precedentemente inviate. Si riporta di seguito la sinossi del progetto.

Cordiali saluti.

IL DIRETTORE SCIENTIFICO *sostituto*
prof. Alessandro Ventura
- firmato digitalmente -

IL DIRETTORE GENERALE
dott. Gianluigi Scannapieco
- firmato digitalmente -

"Genetics of senses and related diseases"

PI: prof.Paolo Gasparini

Project:

Our senses play together in almost all our daily activities and sensory deficits (including diseases) contribute to loss of autonomy and are associated with cognitive impairments, anxiety, depression, largely compromising quality of life. Here we propose to achieve a thorough understanding of the molecular and genetic bases of sensory deficits in the Italian population using a convergent methodology that integrates data coming from large population collections (environmental, lifestyle, deep phenotypes, etc.), cases-controls cohorts, families with probands affected by a sensory disease, with "omics" data, functional "in vitro" and "in vivo" studies in a very integrated and innovative way never before applied to the study of sensory deficits. Elucidating many new biological/genetics aspects of sensory deficits in an unbiased way could lay the foundation for a thorough understanding and provide tools for their early diagnosis and clinical management.

In particular as regards to hearing, Hearing Loss (HL) is the most common sensorineural disorder characterised by a partial or total inability to hear and it is currently untreatable. For a child, hearing and speech are essential tools of learning, playing and developing social skills. Children learn to communicate by imitating the sounds they hear thus, if they have an undetected and untreated hearing loss, they can miss much of the speech and language around them leading to delayed speech/language development, social problems and academic difficulties. HL affects two in every 100 children under the age of 18 and it is characterized by clinical and genetic heterogeneity making much more complicated a molecular diagnosis. In the inherited forms GJB2, GJB6 and MTRNR1 mitochondrial genes play a major role worldwide although with huge differences in prevalence among populations. For more than 60% of cases the molecular diagnosis is not defined thus, there is a strong need to further explore the landscape of causative mutations/genes. Moreover, depending on the gene involved, the onset, the severity and the prognosis of the disease can vary a lot. Thus, Next Generation Sequencing (NGS) has been largely applied to allow an early diagnosis and moving towards a personalized therapy. In the last 5 years approximately 100 Italian families have been already analysed by our group using Targeted Re-Sequencing (TRS) of 113 HHL-genes followed, in negative cases, by Whole Exome Sequencing (WES) and by in vitro and in vivo validation of new HHL-candidate genes. The major aims of this part are: ***A1. Definition of a molecular picture of HL by screening of new cases***; ***A2. Identification of new genes mutations involved in HL***; ***A3. Functional validation of mutants by in vitro and in vivo studies***.

As regards taste and food preferences, it is now known that variations in genes coding for taste receptors are responsible for individual differences in taste perception. These differences, affecting food choices and eating habits, have also shown long-term health implications, especially for diet-related illnesses such as obesity and diabetes. Moreover, in recent years it has emerged that taste receptors present in the oral cavity are also found in the gastrointestinal tract and in the airways where they perform different functions than the taste. In the gut, taste receptors seem to help drive digestion or refuse of food, while in the airways they seem to be involved in defense responses from inhaled and potentially toxic extraneous substances. In light of this, it is increasingly evident that further studies are needed to better understand the genetic and environmental factors that may affect taste perception and consequently the dietary preferences, but also the role of taste receptors in various body regions Their connection with the state of health. The present study is therefore aimed at studying the complex relationship between genetics, nutrition and health, with particular reference to the impact of taste perception and food preferences as an effective indicator of long-term effective consumption. This part of the project will be divided into the followingaims: ***A4. Identification of genes responsible for taste perception and food preferences; A5. Study of the influence of genes involved in taste perception on eating behavior; A6. Impact of phenotypes (including metabonomics marks) and genes on the health status including the assessment of diabetes, obesity, caries as well as related phenotypes (body mass index, glycemia, insulin)*.** In addition, in the light of recent discoveries, other pathologies such as respiratory and gastrointestinal diseases will also be considered.

Finally, olfactory dysfunction is common among older adults (24% in adults aged > 70) affecting either overall perception as well as single preferences of odorants, but also several syndromes (i.e. Kalmann)

present with smell dysfunction. The deficit affects safety, nutrition, quality of life. More importantly, the decreased sense of smell is an early symptom of neurodegenerative diseases such as Parkinson (PD) and Alzheimer but has been also found in patients suffering from Autism. Moreover, transcriptome studies in mice revealed that olfactory receptor (OR) gene expression and repertoire varies across developmental stages and decreases with age. A recent study suggests that the differential expression of ORs in elderly may play a role in the sensitivity to their agonists, thus complementing the role that OR allelic variation play on olfactory phenotypes (i.e. odor intensity, odor valence, detection threshold, and food preferences). Interestingly, the rs6591536 genotype of OR5A1, one of the most highly expressed ORs in the human olfactory mucosa, and personal unpublished data), predicts ~96% of the sensory acuity for its ligand beta-ionone. Because the rs6591536 genotype is also affecting the liking for foods containing beta-ionone, it is conceivable that highly expressed ORs can be used as targets to modulate food choices and intake. By this way it would be possible to improve the quality of life and health status of patients. This part of the project will be divided in the followig aims: ***A7. Identification of olfactory genes involved in food preferences; A8. Use of olfactory genes/proteins as targets to modulate food choice and intake (i.e. innovative approach to fight against overweight and obesity).***

Finally, we will also try to use the large database available to combine phenotype's data of the three senses all together and better understand ***how they play together in our daily life (A9).***

To reach the projects aims, we will explore:

1) **epidemiological data and environmental factors** on large and unique dataset characterized by different inbred and outbred populations (approx. 10.000 individuals) for which a very large number of information (personal, clinical, instrumental, environmental as well as genetic/genomics data) including sensory phenotypes of interest has been already collected;

2) **genetics/genomics analysis**, based on the large unique dataset above mentioned as well as on collections of cases and controls suffering from HL, diabetes, autism, etc. already available to identify loci, variants, genes and pathways underlining single sensory deficits and possible pathways underlying multiple sensory deficits. We will investigate: i) genetic associations by GWAS carried out in cohorts already collected to identify new loci/genes; ii) individual genomes (by genotyping, WES, and WGS) to identify variations in genes, iii) validate these genes/variants *in silico* (i.e. protein modelling), *in vitro* (i.e. cell lines) and *in vivo* (i.e. animal models such zebrafish), iv) search for expression quantitative trait locus (eQTL) using public databases, v) identify biological pathways and associate them either to sensory phenotypes and/or possibly related phenotypes such as overweight, obesity, diabetes, autism, etc.

3) **metabolomics marks** in a subset of people/patients carrying a deeper analysis on sensory target tissues (i.e. taste and smell) providing additional data on direct and indirect changes that may occur in sensory perception. In particular, we will analyse metabolomics data from sera and saliva of normal subjects and patients

4) **molecules that may be able to modulate genes/proteins** and stimulate appetite or recover the sensory deficit *"in vitro"* and *"in vivo".*

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Duration: 3 years

Other collaborators:

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