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GENETICAL PROJET

1) **Prof. Zollino, how long have you been a member of RING 14 scientific commitee, and why did you join?**

I have been a member of the Scientific Commitee of Ring 14 International Association since its establishment in 2002.

2) What is your specialization and what type of scientific activity do you carry out?

I am a doctor specializing in Medical Genetics, with a specific field of scientific interest for the matter of psychomotory retardation, with specific reference to the conditions caused by chromosomal abnormalities . Within this field, I developed clinical and laboratory competences connected with the use and interpretation of molecular cythogenetic techniqyes, like array (FISH)-CGH (Array-Based Comparative Genomic Hibridization).

3) The synromes of chromosome 14 have a genetic basis, for this reason the first studies performed in field started from the genetic environment. What has been done in these years of Ring 14 history, where did the study start from, with what methodology and results?

When we started studying the Ring 14 syndrome, as the syndroms caused by the linear deletions of chromosome 14, the scientific knowledge on these conditions was very poor and the cases were limited to few individuals. The study made use of both genetic analysis and a critical clinical evaluation, arranged on the competence of the multiple specialists who make up the Scientific Committee of the Association. The techniques of genetic investigation included:
- a standard chromosome analysis conducted on a great number of cells, aimed to ascertain the existence and the average of mosaicism

- The FISH analysis, with multiple probes, integrated and subsequently replaced by a-CGH analysis, aimed to ascertain the entity of deletion, both in case of ring or linear deletions

- the analysis of segregation of micro polymorphic satellites, to investigate the parental origin of rearrangement (which could have arisen either on the father chromosome or on the mother chromosome) hence on the possible contribution of an unbalance in the genomic imprinting, since the chromososme 14 contains genes subject to imprinting (i.e. the to differentiated expression on the chromosome of paternal or maternal origin)

The results achieved up-to-date, object of a scientific publication on an international review (American Journal of Medical Genetics), may be summarized in the following points:

- the distinctive clinical signs of the Ring 14 syndrome are psychomotory delay, epilepsy, often with littlereaction to treatment, a peculiar appearance of the face, which is however limited to the cases where the ring lost part of the genetic material in its context, retinal abnormalities;
- all the children affected by Ring 14 are mosaic, on blood cells, with a line featured by complete monosomy for chromosome 14;

- the problem of psychomotory delay and epilepsy is independent from the loss of genetic material in the ring context. In fact, a relevant percent of ring cases is “complete”, i.e. no loss of informational genetic material, but epilepsy is still however present;
- the pathogenetic mechanism causing epilepsy (epilepsy is the most important clinical sign, which affects the prognosis of psychomotory delay) does not appear to be the lost of genes, but a transcriptional function of genes, more preserved on the ring, triggered by the ring configuration of the chromosome;
- from an analysis of correlation genotype-fenotypo with linear deletions of chromosome 14, the signs “epilepsy” and “retinal abnormalities” have been mapped in the proximal region of the chromosome, and the gene *FOXG1* has been described as the strongest candidate for epilepsy.

4) How does the genetic research progress? Are there new studies and methodologies?

The new research, already started at our Istitute of Medical Genetics of University Cattolica of Rome, is being articulated on the following aspects:

- chromosome analysis, and array-CGH, on skin fibroblasts of a group of children wiith ring 14;
- analysis of expression, at mRNA, of the gene *FOXG1*, both on limphoblastoid cells and skin fibroblasts;
- quantification, on the same cells, of proteine FOXG1;
- analysis of expression of all the genes, at mRNA level, with specific reference to the genes located on chromosome 14.

These new investigations aim to verify which metabolic patterns may be altered by the transcriptional disfunction of the genes expressed in the CNS and if some of these patterns are susceptibile to be drug-regulation.

5) How important is to finance the research on rare syndromes and which challenges await RING14 in the future?

The financing of research is essential, as it has been in the past which allowed to achieve the current results, innovative in the scientific aspect, and allowed to plan the new research in progress.