

## WHY WAS OUR SUPPORT GROUP CREATED?

Our association was founded in 2002 starting from the RING14 syndrome, from which our name. Subsequently, we included all the syndromes caused by rearrangements of chromosome 14 (deletions, translocations, duplications...). At the moment, there are no other support groups concerned with these pathologies, making it very difficult for parents to exchange experiences and information. Being parents of a child with a rare disease is a challenge: besides trying to face all the problems related to the symptoms of the disease and struggling daily against frequent emergency situations, there is nobody able to tell us exactly what will happen, which are the best treatments, which tests should be done, what will be our child development and which will be his/her quality of life. People affected by these chromosome syndromes, their families and caring doctors, at present, have few instruments capable of providing complete and exhaustive information on all possible symptoms arising from those pathologies.

## AIMS AND PURPOSES OF OUR ASSOCIATION

**IDENTIFYING** and connecting all families with children affected by the Ring14 syndrome and all the aberrations associated to chromosome 14, in order to offer them the support of our Association letting them know that they are no longer alone and to supply, through our web site, a valid instrument of communication, information and exchange of experiences.

**ESTABLISHING** the first medical and scientific "Data Bank" on those rare syndromes, because only in this way it will be possible to detail the description of signs and symptoms concerning syndromes of chromosome 14 creating in such a way a real clinical picture which is at present only partially described in the specific international publications.

**DESIGNING** a route/protocol of medical survey for all aberrations of chromosome 14, investigating the correlations between clinical manifestations and molecular genetic changes.

**PROMOTING** all social, political and scientific activities for diagnosis and research concerning syndromes associated to all aberrations of chromosome 14.

**COLLECTING** funds to promote scientific research, also by funding scholarships, in order to obtain more and better information aiming to define a suitable program for a proper treatment of syndromes associated to all aberrations of chromosome 14 and for the physical, mental and expressive development of people affected by that pathology.

## SCIENTIFIC COMMITTEE

### Dott. Elvio Della Giustina

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### Prof. Marcella Zollino

Responsible of the Cytogenetics and Molecular Cytogenetics Service Università Cattolica Sacro Cuore Roma (Italy).

**CREATING** a network of consultants including doctors, scientists, health workers involved in the problems related to genetic syndromes associated to all aberrations of chromosome 14 in order to offer a better general assistance

## WHAT IS THE RING14 SYNDROME?

RING14 stands for an aberration of chromosome 14 which takes a ring shape owing to the fusion of the two ends of the short and long arm. The fusion takes place from two breaking events, one at the end of the short arm and the other one at the end of the long arm, usually with the consequent partial loss of genetic material at both ends. The anomaly can involve all cells, or it can be in a mosaic state with a cell line which has lost the ring, leaving only one chromosome 14 (monosomy 14).

The chromosome aberration RING14 is responsible for a syndrome characterized by motor and mental retardation and multiple physical anomalies. The initial diagnosis of RING14 syndrome is usually performed by a simple chromosome analysis.

## OTHER ANOMALIES OF CHROMOSOME 14

Partial deletions, translocations

Chromosome 14 can be involved in other structural anomalies, such as interstitial deletions of the long arm and balanced or unbalanced translocations, in which the chromosome remains linear and does not rearrange in the shape of a ring. Clinical signs associated with partial deletions include once again motor and mental retardation and multiple physical anomalies, which are in part similar to the clinical manifestations associated with ring 14. Also in these cases, the preliminary diagnosis usually arises from a simple chromosome test.

UPD(14)

In other cases, chromosome 14 anomalies associated with specific clinical conditions are not structural but functional.

We refer here to situations in which chromosome 14-specific material is fully preserved, but both chromosomes 14 come from the same parent, causing uniparental disomy for chromosome 14 (UPD(14)), of either maternal or paternal origin. Clinical manifestations are quite different in the two conditions.

In UPD(14) of paternal origin clinical signs include severe growth delay, peculiar conformation of skull and face, thoracic deformity, anomalies of the abdominal wall, mental retardation and motor delay. Pregnancy is often complicated by polyhydramnios. In UPD(14) of maternal origin clinical signs are less severe and include hypotonia, feeding problems during the first years of life, mild mental and motor retardation, short stature, small hands and feet. Typical of this condition is the association of short stature and obesity at the age of 7-9 years. The majority of UPD(14) cases ascertained so far are associated with balanced Robertsonian translocations, most frequently t(13;14) translocations, but an increasing number of cases are being reported in association with normal karyotype. For that reasons, diagnosis cannot be reached through a simple chromosome analysis, but specific molecular tests are needed. All syndromic conditions caused by structural or functional anomalies of chromosome 14 are rare. However,

their frequency is underestimated, most likely, with particular regard to the RING 14 syndrome. In fact, physical anomalies are often very mild and growth delay may be mild or absent. For all these reasons, the chromosome test can be delayed or even missed. The clinical and genetic characterization of all these conditions is possible only by analysing a large series of patients. This analysis can provide important insights in improving not only the general knowledge of these conditions, but also the proper diagnostic procedures and treatment.

## WHICH ARE THE SYMPTOMS OF THE RING14 SYNDROME? WHICH ARE THE SYMPTOMS OF 14Q LINEAR DELETIONS?

As to RING14 syndrome, the most constant symptoms concern the central nervous system and the retina even if they change in numbers and gravity case by case. The entity of mental and motor retardation and hypotonia is in fact variable and also microcephaly may vary. Also speech, generally compromised, may vary. The retina may be hyperpigmented and may show small white-yellow stains in the mean periphery, the same stains involve the macula; cataract may appear. Epilepsy is constant, it appears early (even in the very early weeks/months of life) and consists of generalized or partial seizures, probably of fronto-temporal origin; its pharmacological control may result difficult and it may have a "moody" course with long periods with only few seizures; status epilepticus, mainly partial, is of frequent occurrence. Dimorphisms include: flat occiput, high forehead with prominent sagittal suture, hild palpebralptosis, epicanthic-folds, elongated face, large root and round tip of nose antverted nostrils, long philtrum, low set ears with big lobe and prominent antehelix, microretrognathia, short neck; more seldom lymphedema on the back of hands and feet. Intrathoracic and intra-abdominal organs are normally developed. Hyperpigmented skin spots, like scrub white coffee-coloured, may be present. An immunoglobulin deficiency (IgA of surface) has been noted with a high risk of respiratory and, may be, gastrointestinal infections. Linear partial deletions of chromosome 14, at least those concerning the end part of the long arm, are associated,



further to the mental and motor retardation, to physical outlines similar to those present in RING14 syndrome; while "epilepsy" and "hyperpigmented retina" are usually absent.

#### HOW CAN RING14 SYNDROME AND OTHER STRUCTURAL ANOMALIES OF CHROMOSOME 14 BE DIAGNOSED?

With respect to the RING14 syndrome, the preliminary genetic test is suggested by the typical clinical manifestations, including typical physical anomalies, early seizures, motor and mental retardation and retinal anomalies.

It is important to notice that, even if all the above mentioned clinical signs cannot immediately suggest this specific syndromic condition, they are fully consistent with a quantitative chromosome imbalance, leading to the chromosome test. The "RING14" anomaly can be easily diagnosed by a conventional chromosome analysis, which can be performed everywhere. However, its fine definition at a molecular level needs further genetic tests, that are usually carried out in specialistic centres. Electroencephalogram (EEG) is fundamental for epilepsy seizure control, but has no diagnostic function. CAT (Computerized Axial Tomography) scan and MRI (Magnetic Resonance Imaging) Usually show a normal cerebral structure, but they can reveal some critical focal atrophic anomalies often located in the temporal lobe, a dysplasia-hypoplasia of the corpus callosum, a dilatation of the lateral ventricles. Vitreous body and retina examination tests, even in the periphery, add a relevant diagnostic element. Potential evocates and electroretinogram ERG resulted always normal. Ecography examination tests of internal organs add a relevant diagnostic element. Also the preliminary diagnosis of the remaining structural anomalies of the chromosome 14, including partial deletions, is performed by a conventional chromosome analysis, that is suggested by the association of mental and motor retardation and physical anomalies. Also in these cases the proper molecular definition needs further analyses in specialistic centres. Clinical signs can vary in individual patients. Accordingly, different diagnostic tests can be needed in different patients. On the first diagnosis, it is however recommended to perform a the fundus oculi (expected normal) examination, an EEG and an endoabdominal ultrasound examination.

#### CRYPTIC CHROMOSOME ANOMALIES

It is important to notice that the recent molecular cytogenetics techniques, such as telomere analysis and the "microarray-CGH" technique, is improving the genetic diagnosis of constitutional conditions with mental retardation and multiple physical anomalies that are associated with apparently normal chromosomes. Small quantitative chromosome anomalies, including subtle chromosome 14 deletions, can be undetected by a conventional chromosome analysis, which resolution is of about 5 megabases, but they can be detected by molecular cytogenetics techniques only. Therefore, if clinical signs are consistent with a chromosome anomaly but conventional chromosomes are apparently normal, it is recommended to go on with the help of these techniques in specialistic centres.

#### HOW COULD YOU HELP AND CONTACT US?

- By taking part in our Association's activities, expressing your availability by getting in touch with our Association
- By promoting the knowledge of our Association and of the rare syndromes we deal
- By subscribing and yearly renewing your membership card
- By a voluntary gift to be made by bank transfer to:

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associazione internazionale

Per la ricerca sulle malattie neurogenetiche rare

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Ha collaborato alla realizzazione di questi piegevoli



Photo: Michel Bussy



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