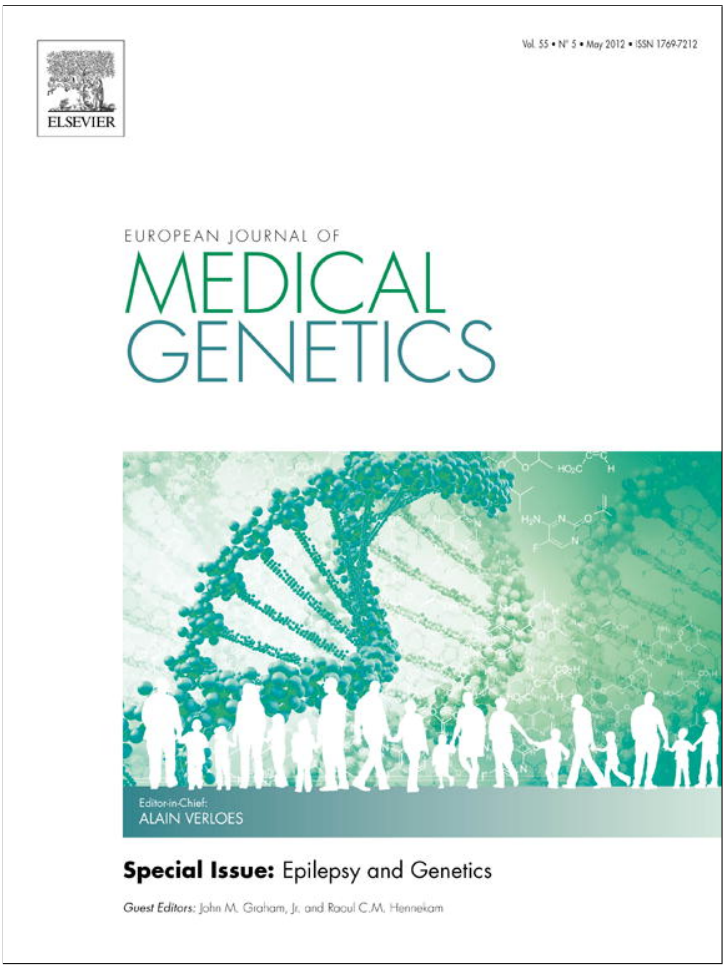

European Journal of Medical Genetics 55 (2012) 374–380

Contents lists available at SciVerse ScienceDirect

European Journal of Medical Genetics

journal homepage: http://www.elsevier.com/locate/ejmg

Review

The ring 14 syndrome

Marcella Zollino [a], Emanuela Ponzi [a], Giuseppe Gobbi [b], Giovanni Neri [a,*]

[a] Istituto di Genetica Medica, Università Cattolica Sacro Cuore, Roma, Italy
[b] UOC di Neuropsichiatria Infantile, IRCCS Istituto delle Scienze Neurologiche, Bologna, Italy

ARTICLE INFO

Article history:
Received 2 December 2011
Accepted 27 March 2012
Available online 14 April 2012

Keywords:
Ring chromosome 14
Phenotypic map
Focal epilepsy

ABSTRACT

The ring 14 syndrome is a rare condition, whose precise clinical and genetic characterization is still limited. This review summarizes literature data and it describes our own experience with 27 patients with ring 14 syndrome. Clinically, the ring 14 syndrome is characterized by a recognizable phenotype of shortness of stature, distinctive facial appearance, microcephaly, scoliosis, and ocular abnormalities, consisting mainly of abnormal retinal pigmentation, but also retinitis pigmentosa, strabismus, glaucoma, and abnormal macula. Virtually all patients are intellectually delayed, with aggressive and hyperactive behavior in some. Drug-resistant, mainly focal in type, epilepsy is another highly consistent finding. In our own sample of patients the ring was complete, with no apparent loss of chromosome material, in 6/27 cases, while it showed a small terminal deletion, varying in size from 0.3 to 5 Mb, in the other 21. In two of these a cryptic 14q duplication of 2.5 and 9.7 Mb, respectively, proximal to the deleted segment, was also identified. Deleted rings were 75% paternal and 25% maternal in origin. UPD (14) was excluded in all cases. Based on literature review of linear deletions, affecting either the proximal or the distal 14q region, we could deduce that retinal abnormalities and epilepsy map within the proximal 14q11.2- q12 region. Because this region is preserved in all patients with ring 14, we speculate that genes residing in the proximal 14q interval are disregulated through heterochromatinization spreading from the adjacent short arm of the chromosome. Behavior disorders and susceptibility to infections can be assigned to the 14q32 region, haploinsufficiency being the most likely underlying mechanism.

1. Introduction

Ring chromosome 14 syndrome is a rare genetic condition first described in 1971 by Gilgenkrantz et al, with over 70 cases reported so far [1–10]. Although there is general agreement that consistent clinical manifestations include typical facial appearance, intellectual disability, retinitis pigmentosa and seizures, fine characterization of both the clinical phenotype and the basic genomic defect is still limited. More importantly, pathogenic mechanisms are unknown, with particular regard to the severe, and usually drug-resistant, seizure disorder. A question also to be addressed is whether imprinting disturbances can play a role in the final phenotype, since a cluster of imprinted genes reside on 14q32.2, including the maternally expressed *MEG3*, and the paternally expressed *DLK1* [11]. Notably, genotype–phenotype correlations are complicated by the mitotic instability of the ring itself, that can cause impaired cell turnover and cell death.

In this review we analyze a total of 27 personally observed subjects with the ring 14 syndrome, 20 of whom were previously reported [10]. Clinical manifestations are compared with those of 39 literature cases of ring 14 syndrome, for whom relevant clinical information are available [2–9], and of 51 subjects with a linear 14q deletions, encompassing either the proximal 14q11-q13 ($n = 20$) [10,12] or the distal 14q24.1-q32.3 ($n = 31$) region [2,5,10,13,14,15], with the purpose of establishing a phenotypic map of the main component manifestations of the ring 14 syndrome. In evaluating our findings in comparison with those of the literature we speculate on whether haploinsufficiency and/or gene silencing represent the underlying mechanisms for specific clinical manifestations.

2. Personally observed ring 14 patients

These patients ($n = 27$) were examined at clinics during meetings of the ring 14 family support group. Consent forms approved by the local IRBs were signed by parents or legal guardians, regarding both physical examination and performance of genetic tests. Of these, 15 were males and 12 females, aged 1–36 years. Clinical analysis included physical examination, neuropsychological evaluation, brain MRI, EEG studies, and fundoscopic examination in all patients, and

* Corresponding author. Istituto di Genetica Medica, Università Cattolica Sacro Cuore, Policlinico "A. Gemelli", L.go F. Vito, 1 00168 Roma, Italy. Tel.: +39 0630154927; fax: +39 0630157223.
E-mail address: gneri@rm.unicatt.it (G. Neri).

1769-7212/$ – see front matter © 2012 Elsevier Masson SAS. All rights reserved.
doi:10.1016/j.ejmg.2012.03.009

a 2–4 years follow-up in most. A formal IQ test could not be administered to a number of patients, due to the severity of the delay, and to the impairment of social skills. The evaluations were mainly qualitative, based on direct observation and semi-structured questionnaires. Whenever possible, Wechsler or Bayley scales were employed.

3. Genetic tests

3.1. Standard cytogenetics

Standard chromosome analysis was performed by RBG banding on 100 cells from peripheral blood lymphocytes, with the purpose of verifying the stability and mosaic status of the ring. This analysis (100 metaphases) was extended to the parents.

In a limited number of patients ($n = 3$) chromosome analysis was also performed on skin fibroblasts by GTG banding (50 metaphases).

3.2. Array-CGH

Array-CGH analysis was performed in 24/27 patients on DNA from peripheral blood lymphocytes using Agilent oligonucleotide-array with an average resolution of about 75 kb, following the manufacturer's instructions (Human Genome CGH Microarray Kit 44B; Agilent Technologies, Santa Clara, CA).

The remaining three patients were analyzed by FISH with a contig specific for the terminal 8 Mb region on 14q.

In three patients high resolution array-CGH was also performed on DNA extracted from skin fibroblasts.

3.3. Microsatellite segregation analysis

This analysis was carried out with the following markers: *D14S583, D14S63, D14S77, D14S1008, D14S267, D14S1007, D14S1419*, and *D14S1420*, with the purpose to establish the parental origin of the deleted ring chromosome 14, as well as possible UPD (14).

4. Genetic results

4.1. Peripheral blood cells

On standard cytogenetics, all patients exhibited the ring on average in 82% of the cells, the remaining 18% being monosomic for chromosome 14, with the only exception of patients 2 and 33, both exhibiting chromosome 14 monosomy in only 5% of the cells (Table 1). On molecular karyotyping, the majority of patients (21/27, 75%) had a small terminal deletion within the ring, varying in size from 0.3 to 5 Mb. In two of them (patients 11 and 35) a cryptic 14q duplication encompassing a 2.5 Mb and a 9.7 Mb region, respectively, proximal to the deleted segment, was identified. Of note, imprinted genes *MEG3* and *DLK1* were never included within the deletion interval, while they underwent duplication in both patients with the del/dup ring (Fig. 2). No deletions of chromosome material within the terminal 14q region was detected in 6 patients (25%). Few cells (not exceeding 3% of those analyzed) from 5 subjects exhibited two copies of the ring, that were linked to each other.

A biparental inheritance of chromosomes 14 was ascertained in all cases ($n = 16$) that underwent this investigation.

Parental origin of the deleted ring was ascertained in 16 patients. It was paternal in 12 (75%) and maternal in 4 (25%). Normal chromosomes were detected in all parents except one, the healthy father of patient 14, who had a ring chromosome 14 in 3 of 288 analyzed cells [10].

4.2. Skin fibroblasts

Genetic analysis was carried out on skin fibroblasts ($n = 50$) from 3 patients, who had, on average, a monosomic cell line in 18% of cultured peripheral boold cells, and a single copy of a deleted ring 14 in the remaining 82%. On skin fibroblasts, monosomy 14 was limited to 1/50 cells (2%) in 2 subjects (patients 13 and 14), who exhibited the ring in all the remaining cells (98%), and it was detected in 9/50 cells (18%) in the third subject (patient 12), who had normal chromosomes in 7/50 cells (14%) and exhibited the ring in the remaining 34 cells (68%). Array-CGH was fully consistent with results on peripheral blood cells.

5. Clinical findings

5.1. Ring 14 patients

5.1.1. The perinatal period

Prenatal history was in general non-contributory and birth was usually at term by normal delivery, caesarean section being uncommon. Measurements at birth were on average normal, intrauterine growth retardation, including true microcephaly being recorded in two patients. Major malformations were consistently absent.

5.1.2. The facial phenotype

At the time of our observation, most patients presented with distinctive facial characteristics, including long and sometimes slightly asymmetric face, full cheeks, high forehead, hypoplastic supraorbital ridges, horizontal eyebrows, deep set and down-slanting eyes with short palpebral fissures, and apparent hypertelorism. The nose was short with a bulbous tip, the philtrum long and the mouth small with downturned corners. However, this peculiar facial appearance was seen only in patients with a deleted ring, and in association with a deletion size greater than 0.65 Mb, but not in patients with 14q terminal deletion smaller than 0.65 Mb or with a non-deleted ring. Facial characteristics of patients with and without deletions larger than 0.65 Mb can be seen in Fig. 1.

5.1.3. Other physical manifestations

Other consistent clinical signs were muscular hypotonia (23/27), microcephaly of postnatal onset (25/27), and ocular problems (18/27) that included retinal pigmentary anomalies in 7 patients, retinitis pigmentosa in one, and cataract, strabismus, maculopathy, glaucoma and myopia in the remaining 10 patients. Scoliosis and café-au-lait spots were noted in some patients. Major malformations were absent. One patient had mild right pulmonary artery obstruction.

Brain MRI was performed in 19 patients and, in agreement with literature data, no consistent cerebral cortex abnormalities were seen in our series. White matter hypoplasia, corpus callosum abnormalities, hippocampal dysmorphisms, and cerebellar structural anomalies were noted in a few cases.

5.1.4. Intellectual and behavioral phenotype

Intellectual disability, mostly of severe degree, was present in all patients except one, who had a non-deleted ring and a milder seizure disorder as well (patient 12). Of importance, a 46,XX normal karyotype was observed in 14% of skin fibroblasts in this patient. Behavior disorders, typically hyperactivity with occasional bursts of aggressiveness, motoric stereotypies, such as hand flapping and echolalia, were also occasionally observed.

A summary of the clinical findings is provided in Table 2, along with review of literature patients. Table 2 also includes patients

Table 1
Clinical-genetic data of personally observed patients with ring 14 ($n = 27$, of which 20 already reported by Zollino et al. [10]).

Pt Code	Sex/ Age (ys)	Cells with 14 monosomy (N/100)	Del Mb	A-CGH	Epilepsy	Hypo-tonia	Micro-cephaly	Language impairment	ID	Facies	Scoliosis	Infections Suscept	Ocular abnormalities	Behavior
1	F/17	20	0.65	del 14q32.33 (105,717,236–106,329,869) × 1	+	+	+	+	+	−	−	+	Strabismus myopia	Quiet
2	F/18	5	2	del 14q32.33 (104,275,679–106,329,869) × 1	+	+	+	+	+	+	+	+	Abnormal macula	Autistic traits
3	M/3	15	<0.2	Normal	+	+	+	+	+	−	−	+	Abnormal retinal pigmentation	Loving, social
4	F/13	23	2.5[a]	Tel 14q- RP11.435F10-	+	−	+	+	+	−	+	−	−	Episodes of self aggressiveness
5	M/4	19	2.5	arr 14q32.33 (103,867,349–106,329,869) × 1	+	+	+	+	+	+	−	−	−	Social/hypercinetic/ aggressive
6	M/10	17	0.3	del 14q32.3 (106,072,471–106,329,869) × 1	+	+	+	+	+	−	+	+	−	Quiet
7	M/36	17	<0.2[a]	Tel 14q+	+	+	+	+	+	−	+	+	Bilateral glaucoma Strabismus	Loving
8	F/23	15	0.65[a]	Tel 14q- RP11.815P21+	+	+	+	+	+	−	+	+	Retinitis pigmentosa	Social/aggressive
9	F/2	21	4.3	del 14q32.33 (102,319,877–106,329,869) × 1	+	+	+	+	+	+	+	−	−	Social, quiet
10	M/1	21	<0.2	Normal	+	+	+	+	+	+/−	−	−	Strabismus	N.A.
11	M/3	19	del 3.2 Mb dup 1.3 Mb	del 14q32.33 (102,319,877–106,329,869) × 1 dup 14q32.2 (100,296,015–101,645,895) × 3.	+	+	+	+	+	+	−	+	Abnormal macula	Quiet
12	F/9	18	<0.2	Normal	+	−	+	−	+/−	−	−	−	Abnormal retinal pigmentation	Social, loving
13	M/5	20	2.5	del 14q32.33 (103,867,349–106,329,869) × 1	+	−	+	+	+	+	−	+	Abnormal retinal pigmentation	Social/aggressive/ hypercinetic
14	M/16	20	1.4	del 14q32.33 (104918795-106,329,869) × 1	+	+	+	+	+	+	+	−	−	Quiet
15	M/1	17	5	del 14q32.31 (101,537,205–106,329,869) × 1	+	+	+	+	+	+	−	+	−	Social, quiet
16	F/1	19	2.6	del 14q32.3 (103,705,675–106,329,869) × 1	+	+	+	+	+	+	−	+	−	Social, loving
17	M/14	19	2.5	del 14q32.33 (103,867,349–106,329,869) × 1	+	+	+	+	+	+	+	−	Abnormal retinal pigmentation	Social/aggressive
18	F/5	17	3.8	del 14q32.33 (102,617,278–106,329,869) × 1	+	+	+	+	+	+	−	−	−	Social/hyperactive/ aggressive
19	M/11	18	<0.2	Normal	+	+	+	+	+	+	−	−	Strabismus, Abnormal retinal pigmentation	N.A.
20	F/2	10	0.65	del 14q32.3 (105,717,236–106,329,869) × 1	+		+	−	+	−	−	−	Abnormal retinal pigmentation	N.A.
31	M/27	27	5	del 14q32.31 (101,537,205–106,329,869) × 1	+	+	+	+	+	+	N.A.	N.A.	N.A.	N.A.
32	M/8	22	0.3	del 14q32.3 (106,072,471–106,329,869) × 1	+	+	+	+	+	−	−	+	N.A.	Autistic traits
33	F/25	5	3.1	del 14q32.3 (103493209-106,329,869) × 1	+		+	+	+	+	N.A.	N.A.	Hypermetropia, astigmatism	Stereotypies, loving
34	M/6	20	<0.2	Normal	+		+	+/−	+	−	−	+	N.A.	Social
35	M/9 IUGR	28	del4.4 Mb dup 9.7 Mb	del 14q32.3 (101,964,365–106,329,869) × 1 dup 14q32.12 (92,031,161–101,895,592) × 3	+	−	+	+	+	+	+	+	Iris coloboma	Autistic traits

36	F/28	IUGR	N.A.	2.2	del 14q32.3 (104,527,022–106,329,869) × 1	+	+	+	+	+	+	N.A.	N.A.			Autistic traits
37	F/3	N.A.	5		del 14q32.3 (101,371,112–106,329,869) × 1	+	+	+	+	+	+	–	Retinal hyperpigmentation			Social, loving

Patients 1–20 were previously reported (Zollino et al., 2009).
ID: intellectual disability.
IUGR: intrauterine growth retardation.
-: Not present.
N.A. not available.
a-CGH: NCBI 36 build probe alignment.
[a] Locus-specific FISH only performed.

carrying 14q linear deletions, who are relevant in establishing genotype–phenotype correlations in ring 14 patients.

5.1.5. The seizure disorder

All the patients experienced epilepsy. To characterize the phenotype, EEG features, and evolution of the epilepsy, a total of 22 patients (13 males and 9 females, aged 26 months to 22 years) were studied in detail. Age at onset, seizure semiology and frequency at onset and at follow-up, drug responsiveness/resistance, and inter-ictal/ictal EEG data were examined. Seizures at onset were of various types, including generalized tonic-clonic, myoclonic-tonic, and clonic, as well as focal with secondary generalization, mainly originating from the mid-temporal and frontal lobe [17]. Soon after onset, epilepsy showed a particularly severe phenotype. During the follow-up, a better definition of a focal onset of seizures, clustering of complex partial episodes with longer seizure-free periods and frequent *status epilepticus* were noted in all patients. No patient had only one type of seizures.

Epileptic manifestations were drug-resistant. Nevertheless, seizures showed a tendency to decrease in late adolescence. We have now 3 seizure-free patients, who at the last neurological follow-up were 20 (2 patients) and 13 years old, respectively. All of them are still taking antiepileptic medications.

EEG abnormalities consisted of slow background activity with pseudoperiodic bursts of generalized slow waves in the early stage, focal fronto-temporal or mid-posterior slow waves with multifocal spikes interposed, and unusual rhythmic, fast recruiting posterior spikes followed by secondary generalization.

5.1.6. Natural history

Most patients experienced marked susceptibility to infections, mainly consisting of respiratory tract infections that required repeated hospitalization. Menarche occurred at 11 years in 3 of 4 adult females, at 13 years in one and menses were reported normal. In the course of adolescence and adulthood, statural growth tended to decelerate and scoliosis was diagnosed in some cases. With age, there was a tendency towards a more quiet behavior, and a milder seizure disorder. The facial phenotype did not seem to change significantly with age.

5.2. Genotype–phenotype correlations, phenotypic map and likely pathogenic mechanisms

We looked for genotype–phenotype correlations by analyzing our patients in comparison with literature patients with ring 14 ($n = 39$) and with a linear 14q deletion affecting the distal ($n = 31$) or proximal ($n = 20$) region. In ring 14 patients the degree of intellectual delay was, on average, severe. It was independent of the presence and extent of the deletion within the ring, but consistently correlated with the severity of the seizure disorder. Of note, patients with a non-deleted ring had a nearly normal psychomotor development in early infancy, but almost all experienced regression after seizures. Although a range of variability was observed, the only patient with a very mild intellectual disability was a mosaic with normal 46,XX cells (patient 12). Typical facial characteristics occurred in association with deleted rings, being almost absent in cases where the ring was either non-deleted or had a very small deletion (<0.65 Mb), suggesting that genes for facial characteristics map to the interstitial, sub-terminal portion of chromosome 14q.

By comparing clinical signs of patients with a ring chromosome with those of patients carrying a proximal or distal 14q linear deletion, we confirmed that seizures and ocular anomalies are attributable to genes located proximally on 14q11q13, as previously reported [10, 16]. Haploinsufficiency of these genes is structural in cases with a linear deletion. On the other hand, given that the

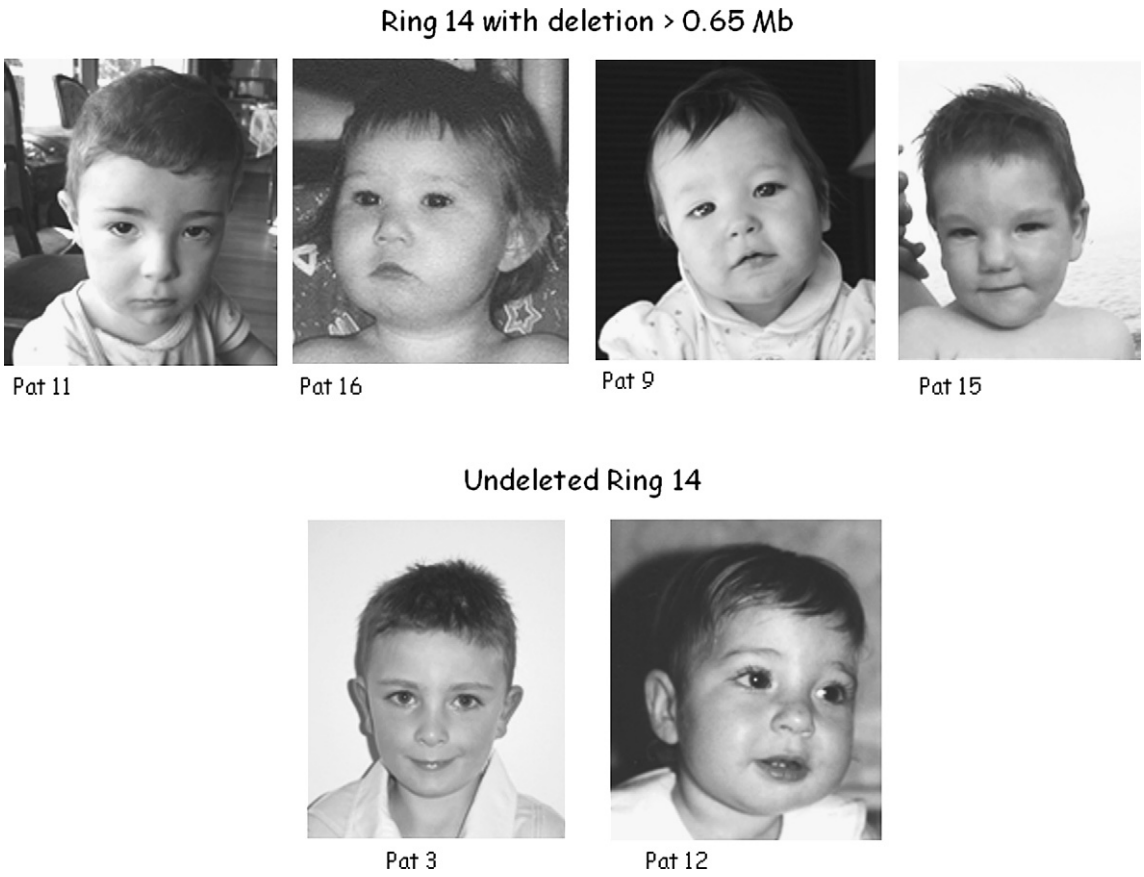

Fig. 1. Facial appearance of patients with ring 14, grouped on the basis of presence or absence of chromosome deletion within the ring. (Formal consent for publication of clinical pictures was obtained from parents).

proximal 14q segment is preserved in all ring 14 patients, one can speculate that genes in this region undergo silencing because of heterochromatin configuration propagating from the adjacent short arm of the chromosome. This hypothesized mechanism is likely limited to the proximal 14q region, due to spatial configuration of the ring. We already assigned genes for behavior disorders and susceptibility to infections to the terminal 14q32.1q32.3 region, based on the presence of these clinical manifestations in subjects hemizygous for this region, due to either linear or ring deletion [10], and we consider that haploinsufficiency is the underlying

Table 2
Clinical findings in ring 14 patients and in patients with 14q linear deletion.

Clinical sign	Ring 14			Linear 14q deletions			
	Literature patients no 39[a]	This report no 27	Tot %	Distal		Proximal	
				Literature patients no 31[b]	%	Literature patients no 20[c]	%
IUGR	10/28	2/27	**21**	9/22	**40**	4/17	**24**
Postnatal microcephaly	23/32	25/27	**81**	12/28	**42**	13/17	**76**
Postnatal growth delay	11/24	18/27	**57**	9/24	**37**	13/18	**72**
Seizures	38/39	27/27	**98**	3/25	**12**	8/19	**42**
Intellectual disability	38/39	26/27[d]	**97**	29/29	**100**	18/18	**100**
Facial appearance with *blepharophimosis short bulbous nose, long philtrum, epicanthal folds, small mouth*	Frequent[e]	16/27	**≈70**	Frequent	**≈80**	0[c]	**0**[f]
Hypotonia	16/27	23/27	**72**	17/24	**70**	12/19	**63**
Retinal abnormalities/visual impairment	13/26	18/27	**58**	0/11	**0**	6/11	**55**
Susceptibility to infections	3/3	21/27	**80**	5/7	71	4/20	**20**
Behavior disorders	n.a.	16/27	**59**	4/4	100	3/20	**15**

[a] Van Karnebeek et al., 2002; Morimoto et al., 2003; Hou, 2004; Schlade-Bartusiak et al., 2005; Knijnenburg et al., 2007; Nucaro et al., 2009; Ville et al., 2009; Guilherme et al., 2010.
[b] Van Karnebeek et al., 2002; Schlade-Bartusiak et al., 2005; Schlade-Bartusiak et al, 2009; Zollino et al., 2009; Youngs et al., 2011; Youngs et al, 2012.
[c] Torgyekes et al., 2011; Zollino et al., 2009.
[d] The only patient with borderline ID was a mosaic for ring 14 (patient 12).
[e] Typical facial appearance is limited to rings with deletion above 0.65 Mb.
[f] Different, but recurrent facial characteristics are described, including round face, large eyes, sloping forehead and broad nasal bridge.

mechanism for these signs. A summary of these observations is provided in Figs. 2 and 3. It should be noted that Fig. 3 is modified with respect to a previous version [10], based on a larger number of observations that supported strong genotype–phenotype correlations only for epilepsy and retinal anomalies with region 14q11q13, on one hand, and for susceptibility to infections and behavior problems with region 14q32.1q32.3.

6. Discussion

The delineation of the ring 14 syndrome in this report is based both on our own partly published [10] findings and on literature data. Our observations are generally in good agreement with those of van Karnebeek et al. [2], with some discrepancies, especially concerning the epilepsy phenotype. Although intrauterine growth retardation was observed only rarely among our patients, prenatal growth delay, including true microcephaly, is described in about 20% of literature patients. On the other hand, there is agreement on postnatal growth delay and microcephaly, seen in the majority of cases. A recurrent pattern of minor facial anomalies is observed, although it is limited to patients with deletions within the ring. The eye involvement usually consists of mild peripheral retinal pigmentation abnormalities, without significant visual impairment. Epilepsy is present in virtually all ring 14 patients. We found no characteristic seizure types or specific ictal/interictal EEG patterns, confirming previous observations [17]. In contrast to the prevalence of generalized seizures described in the early literature, we observed that the epilepsy is predominately focal with frontal and temporal seizures. It is also possible to recognize a rather typical evolution of epilepsy, which may be empirically divided into three successive stages. In stage 1, epilepsy presents with frequent clusters of seizures sometimes before the development of other recognizable clinical features. In stage 2, seizures activity is quite stable but intellectual decline and speech problems become evident. In the final stage, epilepsy tends to decrease in severity and frequency of episodes, up to total absence of seizures in some older patients. Further clinical progression does not seem to occur, but cognitive impairment persists at a moderate to severe degree. Intellectual delay was found in all subjects, except for a girl with low-normal intelligence, and a boy with very mild delay. They both had a ring with no apparent loss of chromosomal material and, more importantly, a less severe epilepsy. It is worth noting that the only patient who had low-normal intelligence, also had a significant number of cells with normal chromosomes in skin fibroblasts. Ring 14 patients are usually good natured, but hyperactive, and with occasional bursts of aggressiveness.

We also reviewed a total of 31 subjects with a linear deletion affecting the distal 14q region (Table 2). The phenotype of these subject differs substantially from that of the ring 14 syndrome patients, being generally less severe and without either epilepsy or retinal anomalies, although the loss of chromosomal material is larger, as previously noted [10]. These patients frequently present with behavior disorders and susceptibility to infections. On the other hand, review of a total of 20 subjects with a linear deletion affecting the proximal 14q region showed that epilepsy and visual impairment are rather frequent in these subjects, leading to hypothesize that genes for both the seizure disorder and visual abnormalities reside in the proximal 14q region. We speculate that genes residing in this region are disregulated by heterochromatization spreading from the adjacent short arm of the chromosome, caused by the ring configuration itself. Interestingly, among a total of 15 patients reported by van Karnebeek et al. [2] with linear deletions at, or distal to, 14q24 band, seizures were uncommon, with the notable exception of one individual with a breakpoint at 14q32.11. One can tentatively infer that another gene for seizures resides in this region. Recently, *SLC8A3*, mapping in 14q24.2 and encoding a sodium-calcium exchanger likely involved in epilepsy, was suggested as an additional candidate gene for seizures, based on the observation of a unique ring 14 patient with discontinuous deletions within the ring, including a 14q24.2 deletion limited to a single BAC clone [8].

From all these observations, we can assume that several genes with a potential role in epileptogenesis reside on chromosome 14, and that pathogenic mechanisms are either gene silencing, through impaired transcription, or haploinsufficiency, through gene deletion.

As to the variable molecular constitution of rings, this seems to reflect their mechanism of origin, which include end-to-end fusion (in cases of complete ring), two breakage events at both chromosome ends, with loss of variable amounts of genetic material, followed by conjoining of the broken chromosome ends (rings with deletion), or breakage at one chromosome end only, followed by interchromatid fusion, production of a dicentric chromosome and breakage within it at telophase [18].

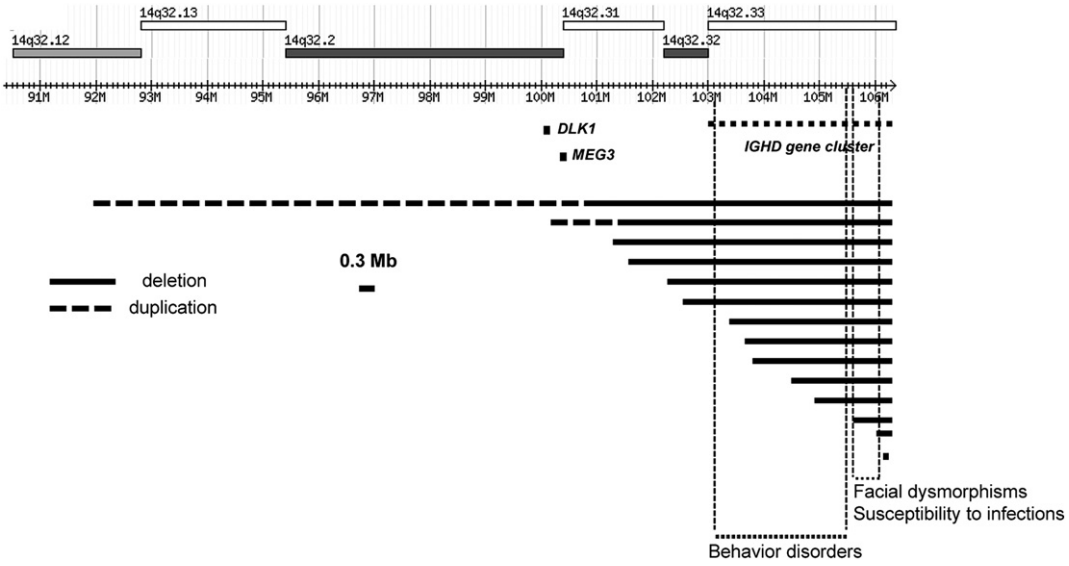

Fig. 2. Histogram of individual deletions/duplications of ring 14 patients (shared deletions are grouped in one symbol) and genetic boundaries for facial dysmorphisms, susceptibility to infections and behavior disorders. Although episodes of aggressiveness and autistic traits were noted in two patients with very small deletions, behavior disturbances usually occurred in association with relatively large deletions.

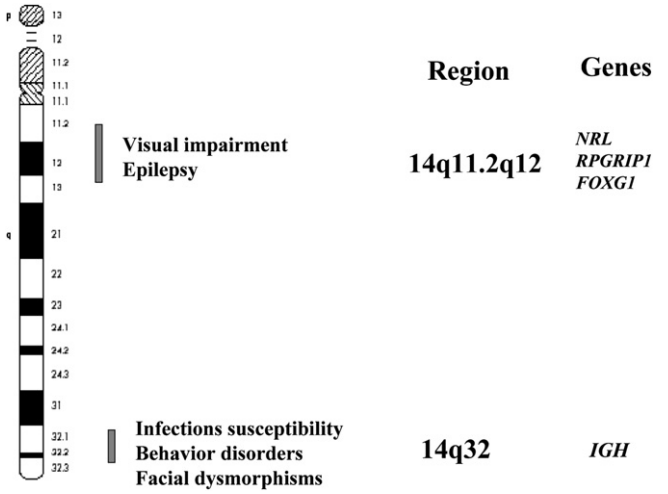

Fig. 3. Phenotypic map of main clinical manifestations of ring 14 syndrome.

Having established a deletion map, as well as genotype–phenotype correlations (Fig. 3), some further considerations are in order. The first thing to point out is that the two most distinctive manifestations of the ring 14 syndrome, namely epilepsy and retinal degeneration, are unlikely to be due to the 14q32qter deletion, given that they are not found in subjects with a comparable linear deletion. We suggest that these traits may be assigned to the 14q11q13 region, containing the retinitis pigmentosa gene *RPGRIP1*, as well as the neural retina leucine zipper gene *NRL* [19]. Also contained in the region is the *FOXG1B* gene, expressed in the developing fetal brain [20]. To support the involvement of this chromosomal region one would have to postulate the action of regulatory mechanisms, such as position effect. The formation of the ring could induce the spreading of heterochromatinization from the short arm of the chromosome down some distance to the long arm. Likewise, we consider that haploinsufficiency of the 14q32qter region is the most likely underlying mechanism for facial dysmorphisms, susceptibility to infections and behavior disorder.

Mitotic instability of the ring is likely to act as co-factor in the pathogenesis of this condition.

The phenotype of the ring 14 syndrome does not seem to be influenced by a parent-of-origin effect, given that microsatellite analysis demonstrated both paternal and maternal inheritance, with some prevalence of the paternal origin. All the rings seem to have formed *de novo*, with the possible exception of one case, where the father was found to be a low mosaic for a ring 14 chromosome in peripheral blood. A possible effect of UPD 14 was also excluded, given that biparental inheritance of the ring and of the normal chromosome 14 was demonstrated in all cases analyzed.

Further studies on the pathophysiology of the ring 14 syndrome should be planned on the basis of the reported findings.

Acknowledgments

We gratefully acknowledge the financial support of the Associazione Ring 14, Reggio Emilia, Italy. We are also grateful to patients and families participating in this study.

References

[1] S. Gilgenkrantz, C. Cabrol, C. Lausecker, M.E. Hartleyb, B. Bohe, The Dr syndrome. Study of a further case (46, XX, 14r), Ann. Genet. 14 (1971) 23–31.
[2] C.D.M. van Karnebeek, S. Quik, S. Sluijter, M.M.F. Hulsbeek, J.M.N. Hoovers, R.C.M. Hennekam, Further delineation of the chromosome 14q terminal deletion syndrome, Am. J. Med. Genet. 110 (2002) 65–72.
[3] M. Morimoto, T. Usuku, M. Tanaka, O. Otabe, A. Nishimura, M. Ochi, Y. Takeuchi, H. Yoshioka, T. Sugimoto, Ring chromosome 14 with localization related epilepsy:three cases, Epilepsia 44 (2003) 1245–1249.
[4] J.W. Hou, Mosaic ring chromosome 14 and monosomy 14 presenting with growth retardation, epilepsy, and blepharophimosis, Chang Gung Med. J. 27 (2004) 373–378.
[5] K. Schlade-Bartusiak, T. Costa, A.M. Summers, M.J.M. Nowaczyk, D. Cox, FISH-mapping of telomeric 14q32 deletions: search for the cause of seizures, Am. J. Med. Genet. 138A (2005) 218–224.
[6] J. Knijnenburg, A. Haeringen, K.B.M. Hansson, A. Lankester, M.J.M. Smit, R.D.M. Belfroid, E. Bakker, C. Rosenberg, H.J. Tanke, K. Szuhai, Ring chromosome formation as a novel escape mechanism in patients with inverted duplication and terminal deletion, Eur. J. Hum. Genet. 15 (2007) 555–584.
[7] Ville D., J. De Bellescize, M.A. Nguyen, H. Testard, A. Gautier, J. Perrier, M. Till, V. Des Portes, Ring 14 chromosome presenting as early-onset isolated partial epilepsy, Dev. Med. Child. Neurol. 51 (2009) 917–922.
[8] A.L. Nucaro, M. Falchi, T. Pisano, R. Rossino, F. Boscarelli, G. Stoico, A. Milia, C. Montaldo, C. Cianchetti, D. Pruna, Ring chromosome 14 mosaicism: an unusual case associated with developmental delay and epilepsy, characterized by genome array-CGH, Am. J. Med. Genet. Part A 152A (2010) 234–236.
[9] R.S. Guilherme, V. de Freitas Ayres Meloni, C.P. Sodré, D.M. Christofolini, R. Pellegrino, C.B. de Mello, L.K. Conlin, A.L. Hutchinson, N.B. Spinner, D. Brunoni, L.D. Kulikowski, M.I. Melaragno, Cytogenetic and molecular evaluation and 20-year follow-up of a patient with ring chromosome 14, Am. J. Med. Genet. Part A 152A (2010) 2865–2869.
[10] M. Zollino, L. Seminara, D. Orteschi, G. Gobbi, S. Giovannini, E. Della Giustina, D. Frattini, A. Scarano, G. Neri, The ring 14 syndrome: clinical and molecular definition, Am. J. Med. Genet. A 149 (2009) 1116–1124.
[11] M. Kagami, Y. Sekita, G. Nishimura, M. Irie, F. Kato, M. Okada, S. Yamamori, H. Kishimoto, M. Nakayama, Y. Tanaka, K. Matsuoka, T. Takahashi, M. Noguchi, Y. Tanaka, K. Masumoto, T. Utsunomiya, H. Kouzan, Y. Komatsu, H. Ohashi, K. Kurosawa, K. Kosaki, A.C. Ferguson-Smith, F. Ishino, T. Ogata, Deletions and epimutations affecting the human 14q32.2 imprinted region in individuals with paternal and maternal upd(14)-like phenotypes, Nat. Genet. 40 (2008) 237–242.
[12] E. Torgyekes, A.L. Shanske, K. Anyane-Yeboa, O. Nahum, S. Pirzadeh, E. Blumfield, V. Jobanputra, D. Warburton, B. Levy, The proximal chromosome 14q microdeletion syndrome: delineation of the phenotype using high resolution SNP oligonucleotyde microarray analysis (SOMA) and review of the literature, Am. J. Med. Genet. 155A (2011) 1884–1896.
[13] K. Schlade-Bartusiak, H. Ardimger, D.W. Cox, A child with terminal 14q deletion syndrome:consideration of genotype-phenotype correlations, Am. J. Med. Genet. 149A (2009) 1012–1018.
[14] E.L. Youngs, J.A. Hellings, M.G. Butler, A clinical report and further delineation of the 14q32 deletion syndrome, Clin. Dysmorph. 20 (2011) 143–147.
[15] E.L. Youmgs, M. Dasouki, M.G. Butler, 14q32 deletion syndrome:a clinical report, Clin. Dysmorph. 21 (2012) 42–44.
[16] M. Zollino, D. Orteschi, G. Neri, Phenotypic map in ring 14 syndrome, Am. J. Med. Genet. A 152A (2010) 237.
[17] S. Giovannini, D. Frattini, A. Scarano, C. Fusco, G. Bertani, E. Della Giustina, P. Martinelli, D. Orteschi, M. Zollino, G. Neri, G. Gobbi, Partial epilepsy complicated by convulsive and nonconvulsive episodes of status epilepticus in a patient with ring chromosome 14 syndrome, Epileptic Disord. 12 (2010) 222–227.
[18] E. Rossi, M. Riegel, J. Messa, S. Gimelli, P. Maraschio, R. Ciccone, M. Stroppi, P. Riva, C.S. Perrotta, T. Mattina, L. Memo, A. Baumer, V. Kucinskas, C. Castellan, A. Schinzel, O. Zuffardi, Duplications in addition to terminal deletions are present in a proportion of ring chromosomes: clues to the mechanisms of formation, J. Med. Genet. 45 (2008) 147–154.
[19] Q. Farjo, A. Jackson, S. Pieke-Dahl, K. Scott, W.J. Kimberling, P.A. Sieving, J.E. Richards, A. Swaroop, Human bZIP transcription factor gene NRL: structure, genomic sequence, and fine linkage mapping at 14q11.2 and negative mutation analysis in patients with retinal degeneration, Genomics 45 (1997) 395–401.
[20] S. Wiese, D.B. Murphy, A. Schlung, P. Burfeind, D. Schmundt, V. Schnulle, M.G. Mattei, U. Thies, The genes for human brain factor 1 and 2, members of the fork head gene family, are clustered on chromosome 14q, Biochim. Biophys. Acta 1262 (1995) 105–112.