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Developing with ring 14 syndrome: A survey in different countries

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Abstract
This study aimed to assess the communicative skills of children and young adults with ring 14 syndrome and linear 14q deletions, investigating the relationships among their language development and their genetic, clinical, psychomotor and behavioural characteristics. Participants were 36 individuals with chromosome 14 aberrations whose parents completed a questionnaire, specifically developed in five languages, to assess their son's/daughter's development. Data analysis showed that chronological age does not account for the high individual variability found in the participants' skills. The comparison between participants with ring 14 syndrome and participants with 14q linear deletions showed that the former were characterised by a higher occurrence of epilepsy, abnormalities of the retina and autism. The participants with smaller amounts of deleted genetic material were those who had a higher level of language development. Because ring 14 syndrome is a rare genetic disease, the collection of data from a large group of individuals could be helpful to create expectations about the possible developmental outcomes of these children.

Keywords: behavioural problems, language development, linear 14q deletions, ring 14 syndrome

Introduction

Rare genetic diseases are chronically debilitating or life-threatening disorders, occurring in fewer than 1 out of 2000 people, as defined by the European Commission on Public Health. Ring 14 syndrome is a rare genetic condition with an unknown prevalence: only 70 cases have been reported so far in the literature (Zollino et al., 2009). This syndrome was first described by Gilgenkrantz, Cabrol, Lausecker, Hartleyb, & Bohe (1971). However, its precise clinical and genetic characterisation has been only recently completed by Zollino et al. (2009). According to this study, at the chromosomal level, people with ring 14 present a characteristic ring-shaped rearrangement of chromosome 14, frequently associated with a deletion within the terminal 14q region (van Karnebeek, Quik, Sluijeter, Hulsbeek, Hoovers, & Hennekam, 2002; Zollino et al., 2009). As underlined by Guilherme et al. (2011) even complete ring chromosomes can result in phenotypic alterations, as the configuration of the ring chromosome could change the gene expression and cause clinical abnormalities. The ring 14 anomaly can be easily diagnosed by a conventional chromosome analysis. However, its fine definition at a molecular level needs further genetic tests, as FISH analysis and array-CGH analysis (Zollino et al., 2009).

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Although phenotypic heterogeneity is very common in individuals with chromosomal disorders (e.g. Kristoffersen, 2008, on cri du chat syndrome; Stojanovik, Perkins, & Howard, 2006, on Williams syndrome), people with ring 14 syndrome typically show a moderate-to-severe degree of intellectual disability. However, the existence of a patient without intellectual disability has been reported by Zollino et al. (2009). With regard to clinical features, Zollino et al. (2009) analysed the characteristics of 20 patients and found that each patient had microcephaly, 14 individuals showed muscular hypotonia and 13 patients showed ocular problems (including a case of retinitis pigmentosa). Data in the literature (Zollino et al., 2009; Specchio et al., 2012) show that all the patients with ring 14 syndrome experienced epilepsy (frequently drug-resistant) with a high variety of seizure types. The onset of epilepsy usually occurs within the first months of life. Behaviour disorders, including hyperactivity and motoric stereotypies, have been found in a large number of patients (Zollino et al., 2009). Moreover, autistic traits (i.e. persistent deficits in social communication and social interaction and restricted, repetitive patterns of behaviour, interests or activities) have been frequently found in children with ring 14 syndrome (D'Odorico, Giovannini, Majorano, Martinelli, & Zampini, 2011).

With regard to physical appearance, people with ring 14 syndrome usually show a distinctive facial appearance, with a long face, high forehead, down-slanting eyes with short palpebral fissures and a small mouth with downturned corners (van Karnebeek et al., 2002; Zollino et al., 2009). As reported by Zollino, Ponzi, Gobbi, & Neri (2012), typical facial appearance is limited to individuals having rings with a deletion greater than 0.65 Mb (1 Mb = 1 million of base pairs, i.e. the building blocks of DNA). Similar clinical and physical features are found among patients with linear 14q deletions, although a striking difference has been found by van Karnebeek et al. (2002) in the occurrence of epilepsy: only 1 out of 10 patients with linear 14q deletion had seizures, whereas 19 out of 20 patients with ring 14 had seizures.

The studies comparing the development of children with ring 14 syndrome with the development of children with linear 14q deletions found that children with ring 14 are generally more severely impaired than the other children (Zollino et al., 2009; D'Odorico et al., 2011). In particular, language development appeared to be more severely impaired in children with the ring 14 condition than in children with the other chromosome 14 aberrations. Moreover, a higher incidence of autistic spectrum disorders has been found among the children with ring 14. However, it must be underlined that the individual variability in children with chromosome 14 aberrations is wide, as shown by Zampini, D'Odorico, Zanchi, Zollino, and Neri (2012) in a longitudinal study on four children with linear 14q deletion, which showed varied outcomes with regard to linguistic and psychomotor development.

With regard to language development, D'Odorico et al. (2011) and Zampini et al. (2012) found that children's linguistic trajectories are negatively affected by the presence of autism or autistic spectrum disorders in children with both ring 14 syndrome and linear 14q deletions. In fact, out of the four children with ring 14 considered in the study of D'Odorico et al. (2011), only the one who did not present autistic traits showed strong language development. Moreover, in their longitudinal study, Zampini et al. (2012) found that in children with linear 14q deletions, only the two children who were diagnosed with autism showed no increasing trend in their communicative skills during the 1-year observation period. The few data on language development in children with chromosome 14 aberrations show that the communicative skills of these individuals are very heterogeneous: some children were unable to reach a verbal level by the time they are 10-years old (D'Odorico et al., 2011), whereas other children were able to produce complex sentences (i.e. utterances characterised by the presence of at least two verbs and consisting of a main clause and a subordinate clause) when they are younger than 8 years (Zampini et al., 2012). Moreover, it must be emphasised that these descriptive data on the communicative development of children with chromosome 14 aberrations have been collected only on Italian-speaking children.

Due to the lack of data on language development in children with ring 14 syndrome and 14q linear deletions, the aim of this study is to assess communicative competence in these children, examining the relationships among language and other aspects of the children's development: their clinical features, their motor skills and their behavioural problems. Both ring 14 syndrome and 14q linear deletions are rare genetic diseases; therefore, they involve a restricted number of people. To have a reliable case report, this study has been focused on individuals with chromosome 14 aberrations living in countries on three continents, including the USA, Australia and several European countries.

Methods

Participants

Participants were recruited in different countries through the International Association Ring 14 (Reggio Emilia, Italy), which aims to promote research on ring 14 syndrome and on the other genetic aberrations associated with chromosome 14.

Thirty-six children and young adults (21 females and 15 males) ranging in age from 1 to 37 years took part into this study. Twenty-two participants were from Europe (11 from Italy, 4 from France, 2 from the UK, 1 from Belgium, 1 from the Principality of Monaco, 1 from Spain, 1 from Switzerland and 1 from Sweden), 10 participants were from the USA, 1 from Canada and 3 from Australia. The high presence of Italian participants is not only presumably due to a higher incidence of these genetic aberrations in Italy but also rather due to the greater number of years of activity of the International Association Ring 14 in its country of origin.

A copy of each participant's genetic report has been collected by the association. All the parents signed informed consent for participation in the study. Genetic analysis shows a ring 14 syndrome (i.e. a chromosomal ring rearrangement) in 24 participants and a linear 14q deletion in 12 patients. Data on the size of the deletions in children with ring 14 syndrome were available for 16 children: 7 participants had a deletion less than 1 Mb, 5 had a deletion ranging between 1 and 3 Mb and 4 had a deletion greater than 4 Mb. With regard to the participants with linear 14q deletions, data on the size of the deleted areas were available for 8 participants: 1 participant had a deletion less than 1 Mb, 3 had a deletion ranging between 1 and 3 Mb and 4 had a deletion greater than 6 Mb. A summary of the participants' characteristics is reported in Table 1.

Procedure

Information regarding the participants' clinical characteristics, development and general behaviour was collected through a questionnaire specially developed for the present project. The questionnaire was created using the online software Survey Monkey (http://it.surveymonkey.com) to be easily completed by the parents of the individuals living in various countries. The questionnaire has been realised adapting other instruments in the field of developmental

Table 1. Characteristics of the 2 groups of participants.

			Chronological age		
	N	Females	M	SD	Range
Ring 14 syndrome	24	12	14	8.99	2–37
14q deletions	12	9	13	6.71	7–30

psychology, taking into account the specific characteristics of the individuals with chromosome 14 aberrations.

The questionnaire was originally developed in Italian and then translated by bilingual persons into English, German, French and Spanish (the languages were selected taking into account the distribution of the families registered in the International Association Ring 14).

The first part of the questionnaire aimed at collecting the clinical history of the participants with chromosome 14 aberrations: personal data (name, date of birth, gender…), education level (i.e. attending no school courses, nursery, kindergarten, primary school, middle school, high school, day centre and other), type and age of diagnosis and possible rehabilitation treatment (e.g. physiotherapy, psychomotor therapy, speech and language therapy). The inventory then focused on the following areas:

- *Symptomatology and medical condition*. In this section, the parents were asked to mark the symptoms exhibited by their son/daughter (e.g. epilepsy, psychomotor impairment, autistic traits and hyperactivity). The presence of epileptic seizures was considered in depth (asking the age of onset, the type of seizures, the use of drugs to control epilepsy) because it is a frequent symptom in individuals with chromosome 14 aberrations.
- *Motor development*. With regard to this developmental area, only one key question was asked of the parents: whether their son/daughter was able to walk by himself/herself. Parents were also asked to give information regarding the age at which their child began walking.
- *Linguistic development*. Both language comprehension and production were investigated. First, the parents were asked if their son/daughter could produce any words. If the participants were not able to use words to communicate with people, the parents were asked to fill in the questionnaire section on preverbal productions (i.e. vocalisations, babbling and protowords). Otherwise, the age of the participant's first word was investigated.

  Another key question in the linguistic domain was about language fluency: the parents were asked whether their son/daughter could speak fluently (i.e. he/she could produce complete sentences, such as: ''yesterday evening I saw a movie at the cinema'', or ''this ice cream is very good''). The aim of this question was to discriminate between children who could communicate with language in a fluent way and children who were in the first stages of language development. For the children with fluent language, the parents were asked to fill in a section on the use of complex sentences and pronouns in their son/daughter's productions.

  In contrast, for the children who did not speak fluently, the ability of using words to communicate with people and the frequency with which they use words was investigated. Moreover, an estimation of the number of words usually produced by the participants was obtained through a section containing a selection of 30 words. Within this list, the parents had to mark the words their son/daughter could spontaneously use (i.e. he/she was able to produce those words in a communicative way and not only in repetition of something said by the adult). The words in this section have been extracted from the list of words belonging to the Italian version of the MacArthur–Bates Communicative Development Inventory (Il Primo Vocabolario del Bambino, Caselli, & Casadio, 1985). Based on the Italian normative data (Caselli, Pasqualetti, & Stefanini, 2007), 10 of these words are characterised by a precocious acquisition (i.e. words usually acquired by children before 18 months), 10 words are usually acquired later (i.e. between 19 and 24 months) and 10 words are characterised by a later acquisition (i.e. after 24 months). The parents were then asked if their son/daughter could put together two or more words to produce a simple sentence (e.g. ''nice baby''). Moreover, the comprehension of simple sentences (e.g. ''stop it'', ''look here'', ''give me a kiss'') and words was investigated. To assess word comprehension, a list of 20 words has been extracted

from the Italian version of the MacArthur–Bates CDI as for the production section: 10 of these words have a precocious acquisition (i.e. before 22 months) and 10 words have a later acquisition (i.e. after 24 months).

Finally, the production of communicative gestures (e.g. requesting an object far from him/her, stretching his/her arms) and symbolic play (e.g. pretending to drive a car or a motorbike) was investigated.

– *General behaviour.* This questionnaire section addressed behavioural problems. The parents were asked if some behaviours of their son/daughter were considered to be problematic. A list of possible problematic behaviours that could be encountered in daily life was introduced to the parents. For each statement, the parents had to note on a three-point Likert scale if there was no such behaviour (0), if this behaviour has been occasionally noticed and this has been a problem (1), or if this behaviour was often shown by their son/daughter and this had to be considered as a problem (2). The list of behaviour problems has been extracted from the ''Nisonger Child Behavior Rating Form'' (Aman, Tassé, Rojahn, & Hammer, 1996), an instrument developed to assess behavioural and emotional problems in children with intellectual disability. The items concerning behavioural problems have been adapted to the specific characteristics shown by people with chromosome 14 aberrations. Five areas of problematic behaviours have been identified: 1 – difficulties in emotion regulation; 2 – oppositional behaviours; 3 – hyperactivity; 4 – inattention; 5 – isolation and autistic traits. For each of these areas, four items (i.e. examples of behavioural problems) were listed.

At the end of the questionnaire, a less structured section with open questions was given to the parents to note personal comments and observations on the development of their son/daughter. In particular, the presence of some regression period was investigated, asking the parents if their son/daughter had shown any regressions in his/her development as a consequence of any particular event (e.g. his/her verbal production had diminished due to an epileptic seizure or a drug intake). Moreover, the parents were asked whether their son/daughter seemed to have improved and to what extent, as a consequence of a rehabilitation therapy, due to drug intake or after having stopped taking a drug.

Data reduction

A large number of variables have been extracted from the questionnaire. In the following paragraphs, we will introduce all the variables considered in the ''Results'' section.

Some of the extracted variables are dichotomous (i.e. they examined either the presence or absence of a particular characteristic). The dichotomous variables considered in data analyses were the following:

– presence of epilepsy;
– presence of abnormalities of the retina;
– presence of psychomotor delay;
– presence of autistic traits;
– presence of hyperactivity;
– ability to walk autonomously;
– ability to use words to communicate with people;
– ability to produce imperative pointing (i.e. pointing used to obtain an object or a desired action);
– ability to produce declarative pointing (i.e. pointing used to share attention with the communicative partner on a particular event or object);
– ability to speak fluently.

Other variables extracted from the questionnaire are estimations of the number of words or gestures produced or comprehended by the participants. The following variables were considered:

- estimation of the number of words produced by the participants (ranging from 0 to 30 words);
- estimation of the number of words comprehended by the participants (ranging from 0 to 20 words);
- estimation of the number of gestures produced (ranging from 0 to 8 gestures);
- estimation of the number of episodes of symbolic play (ranging from 0 to 6).

With regard to the problematic behaviours scale, five scores have been extracted:

- emotion regulation deficit (ranging from 0 to 8);
- oppositional behaviours (ranging from 0 to 8);
- hyperactivity (ranging from 0 to 8);
- inattention (ranging from 0 to 8);
- isolation and autistic traits (ranging from 0 to 8).

Results

Data analyses

First, the relationship between chronological age and all the variables extracted from the questionnaire has been analysed.

Second, we made a comparison between data collected on participants with ring 14 syndrome and data collected on participants with linear 14q deletions. Because group numerosity and age distribution were very different between the two groups of participants, 12 individuals with ring 14 syndrome have been selected to one-to-one match the participants with linear 14q deletions. The matching has been conducted considering the participants' chronological age, and when possible, gender was also taken into account (due to the large presence of females in the group of participants with linear 14q deletions, a perfect matching for gender was not possible).

Third, all the participants with both ring 14 syndrome and linear 14q deletions have been divided into two groups on the basis of their ability to use words to communicate with people. The behavioural and clinical characteristics exhibited by the participants who were able to communicate with words have been compared with the characteristics exhibited by the participants who were not able to use words in their communication.

Finally, the participants have been divided into three groups on the basis of the size of the deletion to verify if a larger deleted part could be related to worse outcomes in children's development. The participants in the first group have a deleted area less than 1 Mb, those in the second group have a deletion ranging from 1 to 3 Mb, and those in the third group have a deletion greater than 4 Mb.

Due to the small number of participants, non-parametric statistical analyses have been performed.

Relationship between chronological age and participants' linguistic and behavioural characteristics

The relationships between the participants' chronological age and the estimations of words and gestures have been computed to verify whether children's linguistic abilities increase with age, as in typical development, or not. No significant correlations (Spearman's *rho*) have been found between age and the estimation of the words produced ($rho = 0.28$; $p = 0.102$) or comprehended

by the participants ($rho = 0.15$; $p = 0.379$). Moreover, chronological age was not correlated with the estimations of gesture production ($rho < -0.01$; $p = 0.985$) and symbolic play ($rho = -0.02$; $p = 0.900$).

In addition, the correlations between age and behaviour problems have been computed in order to verify if the parents tend to consider their older sons/daughters to be more problematic. In fact, it is possible to hypothesise that some behaviours could be more easily tolerated in younger than in older children; however, no significant correlations were found between age and the problematic behaviours scales (all *rhos* ranging from −0.01 and 0.13; all $p > 0.461$).

Comparison between participants with ring 14 syndrome and participants with linear 14q deletions

As mentioned above, a one-to-one match has been performed between the participants with 14q linear deletions and the participants with ring 14 syndrome, due to the differences in the group's numerosity (12 versus 24 participants) and in the range of chronological ages (7–30 versus 2–37). The 12 selected participants with ring 14 syndrome (4 females) had a mean chronological age of 13 years (SD = 6.14), and their ages ranged from 7 to 30 years (refer Table 1 for the characteristics of the participants with 14q linear deletions).

The frequencies with which the participants in both groups showed clinical problems are reported in Figure 1. Pearson's chi-squared analysis showed that the two groups were significantly different in the presence of epilepsy ($\chi^2 = 20.31$; $p < 0.001$), abnormalities of the retina ($\chi^2 = 5.04$; $p = 0.025$) and autistic traits ($\chi^2 = 4.44$; $p = 0.035$), whereas they were not significantly different in the presence of psychomotor delay ($\chi^2 = 3.43$; $p = 0.064$) and hyperactivity ($\chi^2 = 0.75$; $p = 0.386$).

With regard to the frequencies with which the participants showed motor and linguistic skills (reported in Figure 2), Pearson's chi-squared analysis showed that the two groups were not significantly different in all the variables considered (all χ^2 ranged from 0.18 to 2.18; all $p > 0.140$).

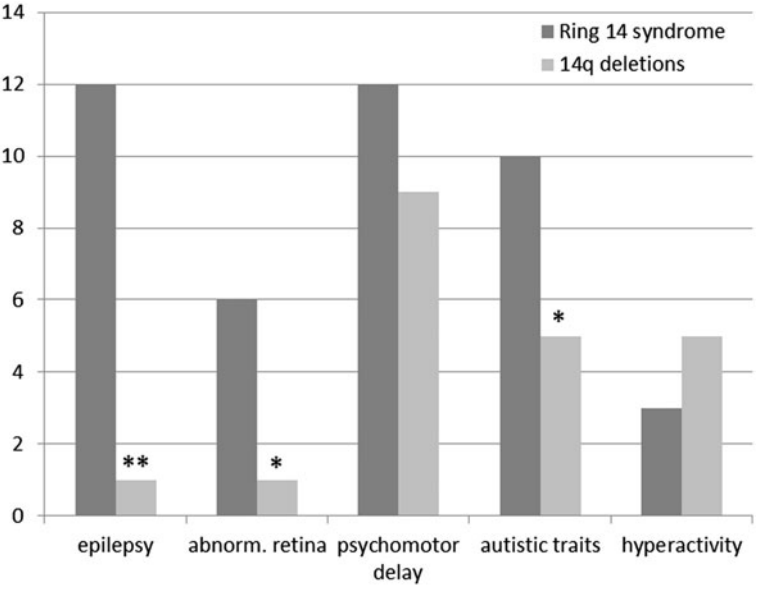

Figure 1. Number of participants with ring 14 syndrome ($n = 12$) or 14q deletions ($n = 12$) showing clinical problems [$*p < 0.05$; $**p < 0.001$].

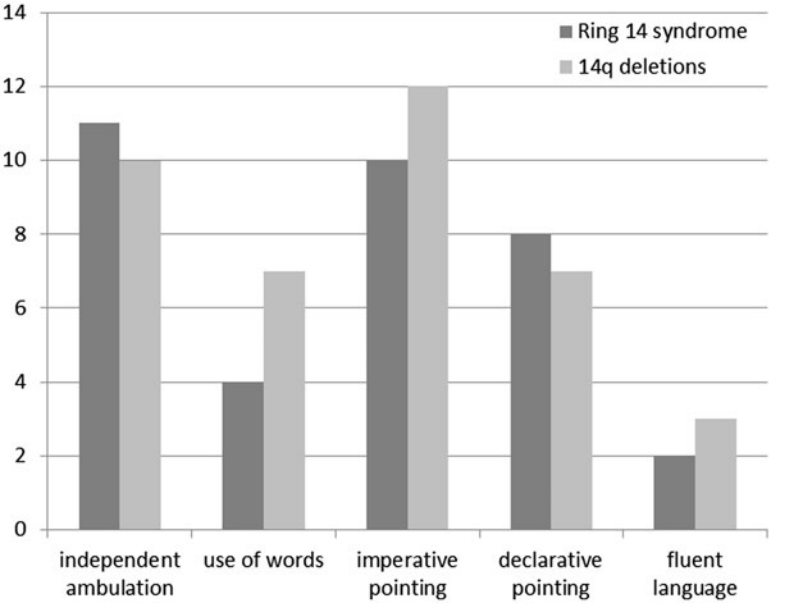

Figure 2. Number of participants with ring 14 syndrome ($n = 12$) or 14q deletions ($n = 12$) who reached psychomotor and linguistic skills.

Table 2. Comparison between participants with ring 14 syndrome and participants with 14q deletions on the scores obtained in the estimations of words and gestures and in the problematic behaviours scales.

		Ring 14 syndrome [$n = 12$]		14q deletions [$n = 12$]		Mann–Whitney	
		M	SD	M	SD	*U*	*p*
Estimations	Words produced [max 30]	10.17	12.50	16.50	13.10	55	0.347
	Words comprehended [max 20]	10.17	7.61	15.58	4.68	42.5	0.089
	Gestures produced [max 8]	4.75	2.77	5.25	2.26	66	0.755
	Symbolic play [max 6]	2.50	2.11	3.24	2.28	54	0.319
Problematic behaviours	Emotion regulation deficit [max 8]	2.33	1.61	2.67	2.06	67.5	0.799
	Oppositional behaviours [max 8]	2.42	2.11	1.75	1.36	85	0.478
	Hyperactivity [max 8]	3.42	1.98	2.58	2.15	91.5	0.266
	Inattention [max 8]	4.33	2.90	4.67	2.39	67.5	0.799
	Isolation and autistic traits [max 8]	3.83	2.08	2.50	1.45	101	0.101

Moreover, the Mann–Whitney test was used to compare the scores obtained in the estimations of gestures and words and in the behaviour problems scales by the participants in the two groups. As reported in Table 2, no significant differences were found between participants with ring 14 syndrome and participants with 14q linear deletions.

Comparison between participants who were able to communicate with words and participants who were not

Independently from the diagnosis, the 36 participants were then divided into two groups on the basis of their ability to use words to communicate with other people: the participants who could

Table 3. Comparison between verbal participants and non-verbal participants on the scores obtained in the problematic behaviours scales.

		Verbal participants [$n = 16$]		Non-verbal participants [$n = 20$]		Mann–Whitney	
		M	SD	M	SD	U	p
Problematic behaviours	Emotion regulation deficit [max 8]	3.06	1.88	2.30	1.87	203.5	0.168
	Oppositional behaviours [max 8]	2.69	1.70	1.85	2.08	209.5	0.116
	Hyperactivity [max 8]	2.13	1.89	3.60	2.19	97.5	0.044
	Inattention [max 8]	4.44	2.39	4.65	2.82	145.5	0.648
	Isolation and autistic traits [max 8]	2.63	1.78	3.80	2.17	109	0.109

Table 4. Characteristics of the participants ($n = 24$) divided into three groups on the basis of the size of the deletion.

				Age		
	N	Females	Ring 14	M	SD	Range
<1 Mb	8	3	7	14	7.87	6.7–29.6
1–3 Mb	8	4	5	15	9.48	3.1–30.4
>4 Mb	8	5	4	10	5.10	2.3–18.8

communicate with words are defined ''verbal'' ($n = 16$), whereas the participants who could not yet communicate with words are defined ''non-verbal'' ($n = 20$). Our hypothesis was that verbal participants should have better psychomotor skills, as found in typical development. The mean chronological ages of the participants in the two groups were not significantly different ($U = 179.5$; $p = 0.539$). A chi-squared analysis showed that the verbal participants were significantly different from the non-verbal participants in their independent ambulation ability: all the verbal participants were able to walk by themselves, whereas six non-verbal participants did not show independent ambulation ($\chi^2 = 5.76$; $p = 0.016$).

The differences in the behaviour problems scales between verbal and non-verbal participants have also been considered. The data, reported in Table 3, show a significant difference in the problematic behaviour of hyperactivity because non-verbal participants are viewed as more difficult to control than the verbal participants.

Relationship between deletion size and clinical and developmental characteristics of the participants

As reported in the participant section, data on the size of the deletion were available for 24 participants. Considering individuals with ring 14 syndrome and 14q linear deletions together, participants have been divided into three groups on the basis of the size of the deletion: less than 1 Mb, ranging between 1 and 3 Mb and greater than 4 Mb. The characteristics of the participants in the three groups are shown in Table 4. No significant differences among the groups have been found in chronological age (Kruskall–Wallis $K = 1.19$; $p = 0.552$) or in the distribution of diagnosis (ring 14 syndrome versus linear 14q deletions; $\chi^2 = 2.63$; $p = 0.269$).

The frequencies with which the participants in the three groups showed clinical problems are reported in Figure 3. Pearson's chi-squared analysis showed that the differences among the three groups were not significant (all χ^2 ranging from 0.34 to 2.82; all $p > 0.244$).

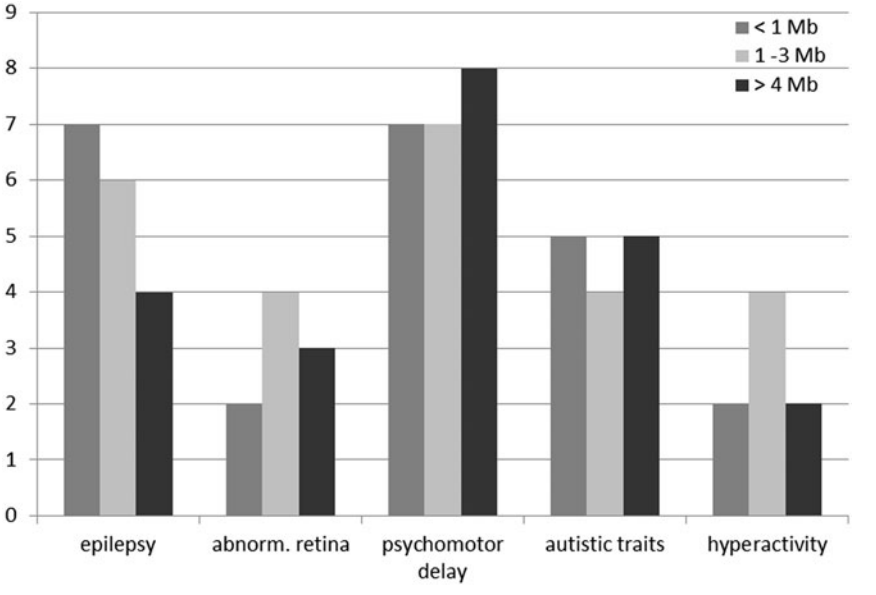

Figure 3. Number of participants with a deletion size less than 1 Mb ($n = 8$), ranging from 1 to 3 Mb ($n = 8$) or greater than 4 Mb ($n = 8$) showing clinical problems.

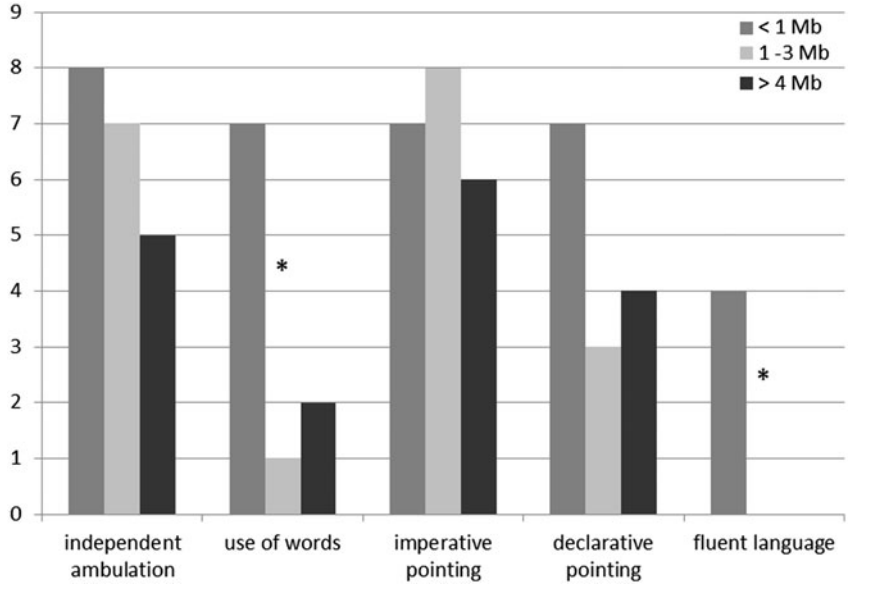

Figure 4. Number of participants with a deletion size less than 1 Mb ($n = 8$), ranging from 1 to 3 Mb ($n = 8$) or greater than 4 Mb ($n = 8$) who reached psychomotor and linguistic skills [$^*p < 0.01$].

With regard to the frequencies (reported in Figure 4) with which the participants in the three groups showed motor and linguistic skills, Pearson's chi-squared analysis showed that the three groups of participants were significantly different in the ability to use words to communicate with people ($\chi^2 = 10.63$; $p = 0.005$) and in the ability to speak fluently ($\chi^2 = 9.60$; $p = 0.008$).

Table 5. Comparison between participants with a deletion size less than 1 Mb, ranging from 1 to 3 Mb or greater than 4 Mb on the scores obtained in the estimations of words and gestures and in the problematic behaviours scales.

		<1 Mb [$n = 8$]		1–3 Mb [$n = 8$]		>4 Mb [$n = 8$]		Kruskall–Wallis	
		M	SD	M	SD	M	SD	*K*	*p*
Estimations	Words produced [max 30]	24.00	11.56	5.13	4.22	7.38	13.36	8.59	0.014
	Words comprehended [max 20]	13.13	9.06	11.25	5.23	10.13	7.68	1.70	0.427
	Gestures produced [max 8]	5.38	3.29	5.13	2.17	3.75	2.32	2.23	0.328
	Symbolic play [max 6]	3.63	2.62	3.25	1.83	1.88	1.64	3.21	0.201
Problematic behaviours	Emotion regulation deficit [max 8]	2.75	1.49	2.88	2.03	1.75	2.12	3.83	0.147
	Oppositional behaviours [max 8]	2.88	2.03	2.00	2.73	2.00	1.77	1.48	0.477
	Hyperactivity [max 8]	2.38	2.20	3.50	2.14	2.75	1.90	1.17	0.558
	Inattention [max 8]	3.88	2.95	4.63	3.16	5.00	2.27	0.73	0.695
	Isolation and autistic traits [max 8]	2.88	2.80	3.38	2.20	3.25	1.67	0.73	0.696

To assess if the three groups were significantly different in the scores obtained in the estimations of gestures and words and in the behaviour problems scales, a Kruskall–Wallis test has been performed. The data, reported in Table 5, showed that the three groups were significantly different only in the mean number of words produced.

Discussion

The aim of this present study was to assess the communicative skills of children and young adults with chromosome 14 aberrations, investigating the relationships among their level of language development and their genetic, clinical, psychomotor and behavioural characteristics.

Participants with ring 14 syndrome or with 14q linear deletions have been recruited in different countries to obtain a group of 36 children and young adults, which is quite large considering that chromosome 14 aberrations are rare genetic diseases. A questionnaire has been specifically developed to assess the participants' communicative development, their clinical characteristics and their possible behavioural problems.

The first aim of this study was to assess if the communicative competence shown by people with chromosome 14 aberrations increases with age, as in typical development. Although the cross-sectional study does not allow the tracking of growth curves, it has to be underlined that significant relationships were found neither between chronological age and gesture production, nor between chronological age and word comprehension and production; therefore, chronological age does not account for the high individual variability found in the communicative development of the participants. In addition, the behavioural problems marked on the questionnaire by the parents were not related to the participants' chronological age. Therefore, it seems that the problematic behaviours do not increase or decrease with chronological age but that some individuals have greater behavioural problems than others.

As, in typically developing children, language and motor development appear to be related in children with chromosome 14 aberrations as well; in fact, the verbal participants were significantly more likely to be able to walk autonomously than the non-verbal participants. However, the non-verbal participants were perceived by their parents as more difficult to control than the verbal ones. In fact, they reached a significantly high score on the hyperactivity scale of the problematic behaviours section. It is possible to hypothesise that, in the absence of verbal language, children and young adults with chromosome 14 aberrations try to communicate their

needs in a less structured way (e.g. with body movements, throwing objects, screaming) that could be interpreted as an hyperactive behaviour.

To test whether the individual differences in the achievement of communicative skills could be explained by the participants' genetic condition, two distinct comparisons were made: the first between participants with ring 14 syndrome and participants with 14q linear deletions and the second among participants with a different size of deleted material (less than 1 Mb, ranging from 1 to 3 Mb and greater than 4 Mb).

Although previous studies found that the developmental profile of children with ring 14 is usually more impaired than that of children with linear 14q deletions (Zollino et al., 2009; D'Odorico et al., 2011), statistically significant differences were found neither between the two groups in the areas of communicative and motor development, nor in the presence of behavioural problems. However, as reported in the literature (van Karnebeek et al., 2002; Zollino et al., 2009), the participants with ring 14 were characterised by a higher occurrence of epilepsy and abnormalities of the retina than the participants with linear 14q deletions. Moreover, autism appeared to be significantly more frequent in the participants with ring 14 syndrome. This result is particularly important because there is evidence in the literature that autism and autistic traits could severely affect language development in children with both ring 14 syndrome (D'Odorico et al., 2011) and linear 14 deletions (Zampini et al., 2012).

Considering the relationships between the participants' skills and the size of the deleted genetic material, a previous study on four children with linear 14q deletions (Zampini et al., 2012) found that a smaller amount of deleted material was not necessarily related to a better developmental outcome. Similarly, in this study, it has been found on a wider group of participants ($n = 24$) that the size of the deleted genetic material could not explain the presence of clinical or behavioural problems; however, a significant difference was found in language development. In fact, the participants in the group with the smallest deletion size (i.e. less than 1 Mb) were those who were more able to use words to communicate with people. Moreover, only in this group were there children and young adults who were able to speak fluently.

A limitation of this study is that data on the participants' competence are based only on parental report. Future studies will aim to directly assess the development of children with chromosome 14 aberrations to deeply analyse their communicative competence. However, although this article has a descriptive aim, the collection of data on a large group of children and young adults with chromosome 14 aberrations could be helpful to the parents and the physicians who take care of these children, because it allows for expectations about the possible developmental outcomes of these children. An in-depth genetic analysis of chromosome 14 will be fundamental to understand which genes are implied in the different aspects considered.

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Declaration of interest

The authors report no conflicts of interest. This study was financially supported by the ''International Association Ring 14'' (Reggio Emilia, Italy).

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