

Original Research

A New Database on Constitutional Human Ring Chromosomes

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Abstract

Human ring chromosomes (RCs) constitute one of the rarest described inborn chromosomal rearrangements. At first, they seem to be just another subgroup of structural chromosomal aberrations like translocations, inversions, or insertions. However, RCs are more complex, as they almost always occur in conjunction with a mosaic karyotype constitution, resulting in mosaic monosomy of the affected chromosome. Most likely due to the latter effect, a genotype-phenotype correlation is still not available. To proceed with solving this problem, a new database is presented here, which summarizes all constitutional RCs—currently, ~1900 cases have been included. The RC-database (<https://cs-tl.de/DB/CA/RC/0-Start.html>) has been included in the ChromosOmics database (<https://cs-tl.de/DB.html>), which already consists of a corresponding collection on small supernumerary marker chromosomes, chromosomal heteromorphisms, constitutional chromosomal breakpoints, and uniparental disomy. Like all others, the RC-database is freely accessible. As first results, the approximate frequency of RCs per chromosome can be assessed, and it can be suggested that the number of RC-carriers with no or minor clinical signs and symptoms is overall ~8%. However, the latter varies clearly according to the chromosomal origin of the RC.



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Keywords

Mosaic; copy number variation (CNV); subtelomeric loss; infertility; ring chromosome

1. Introduction

Human ring chromosomes (RCs) are observed in 1 of 50,000 newborns, with ~2800 newborns per year carrying an RC [1]. Thus, RCs are one of the rarest described inborn chromosomal changes. Recent knowledge on RCs has been summarized in a book [2]. Special attention was given to historical perspectives on human RCs, present knowledge on their formation and cellular behavior, RC diagnostics and research, patient management, family support groups, and family reports. In addition, there is one chapter each on acquired RCs, which are occasionally present in hematopoietic and lymphoid tissues, as well as in solid tumor tissues [2].

The first constitutional RCs were reported in 1962 as X-derived in Turner syndrome [3] and as derived from a chromosome 18 [4]. Previously, RCs were observed in insects (1933) [5], plants (1938) [6], as well as in human tissues, including irradiated human tissues (1958) [7] and human tumors (1956) [8].

Constitutional RCs were first thought to be the either result of a telomeric fusion without gain or loss of genetic material ([9], cases 1 to 20), or due to a fusion of open ends in long and short arm, exclusively with loss of material there ([9], case 27). In between, many other RC variants have been found, which may include terminal deletions and/or subterminal duplications with and without inversions ([9], case 22), or even more complex RCs ([9], case 26).

An intriguing and unique effect of the presence of an RC is that it is practically always associated with a 'dynamic mosaic' karyotype constitution. In the following example ([9], clinically normal mother of the reported family), the presence of an RC derived from chromosome 20 (RC(20)) has been recorded in a female as 46,XX,r(20) [10]. As RCs are mitotically instable, they tend to lead in the carrier to cells

- which lost the RC(20): this is written as 45,XX,-20 and leads to a monosomy 20; and/or
- with an additional RC(20) = karyotype 47,XX,r(20),+r(20); the latter means these cells have a (partial) trisomy of chromosome 20.
- with RCs which duplicate and create dicentric 'double-rings', which leads to (partial) trisomy, too; karyotype: dic r(20;20).
- with a normal karyotype = 46,XX;
 - o in this case the RC(20) either was formed postzygotically,
 - o or cells with a karyotype 45,XX,-20 performed a duplication of the remaining chromosome 20, leading to a uniparental disomy of chromosome 20 in these cells. The latter has been seen in an RC(21) [11].

All these effects make a genotype-phenotype correlation not easy.

As previously for cases with small supernumerary marker chromosomes (sSMC) [12], chromosomal heteromorphisms [13], constitutional chromosomal breakpoints [14] or uniparental disomy [15] the collection of all available corresponding cases in a database turned out to be very helpful, a new database was set up in which all constitutional RCs are summarized. The RC-database

(<https://cs-tl.de/DB/CA/RC/0-Start.html>) [16] has been included in the freely accessible ChromosOmics database (<https://cs-tl.de/DB.html>) and is presented here.

2. Materials and Methods

2.1 Inclusion Criteria for Cases with an RC

Cases with a constitutional RC were included in the database if the RC:

1. was present in a basic karyotype of 46 chromosomes;
2. was not an sSMC with a ring shape;
3. was not formed by the McClintock mechanism.

These definitions were introduced not to include cases in double - in the new database and in the already existing one for sSMCs [12].

These criteria were unambiguous for autosomal and X-chromosome-derived RCs. For RC(Y) only such cases were included, which comprised at least the region Yp11.3 to Yq11.23. In addition, the problem is that in most publications, ring size is not considered in abstracts, which means that many inaccessible papers could not be included yet, but might be updated over time. Finally, ~180 small ring-shaped derivatives of the X- and ~80 cases derived from the Y-chromosomes are already included in the sSMC database [12].

2.2 Sources Screened to Find Literature

To find as many RC cases as possible, the following webpages were used to find potential candidate references:

- <https://pubmed.ncbi.nlm.nih.gov>
- references provided in [2]
- <https://www.malacards.org>
- references in papers providing a review of the literature

Overall, >3500 references were screened for suitability; ~1200 of them turned out to be suitable.

2.3 How Clinical Findings Were Assessed

Clinical findings in RC cases were included in the database in a more summarized manner. This means that rather unspecific and/or atypical aberrant patterns were not included (such as clinodactyly or specific lists of dysmorphic patterns). Features such as those listed for the corresponding RC-subgroup in Orphanet [17] were mainly considered. Infertility, if it were the only clinical feature/reason for chromosomal study in an individual, was considered a minor clinical problem, and the corresponding case was listed as cases without or very mild clinical findings. The same held for most cases, which were somehow affected but were still able to reproduce and/or had normal intelligence.

3. Results

Following the defined inclusion criteria almost 1900 RC cases (yet 1879 cases) could be included into the database on constitutional RCs.

As shown in Table 1 there is an uneven distribution among the RCs derived from chromosomes 1 to 22, X and Y. In Figure 1 the data from Table 1 is sorted according to the frequency of reports on chromosome-specific RCs. Most frequently reported are RCs derived from acrocentric chromosomes and small chromosomes, such as chromosomes 18 and 20.

Table 1 Number of RC-cases by chromosome found in the literature and included in [16].

Chromosome	Number of RC-cases
1	9
2	18
3	16
4	66
5	24
6	46
7	24
8	11
9	44
10	21
11	18
12	13
13	161
14	163
15	148
16	9
17	31
18	247
19	10
20	299
21	143
22	283
X	55
Y	20
Overall	1879

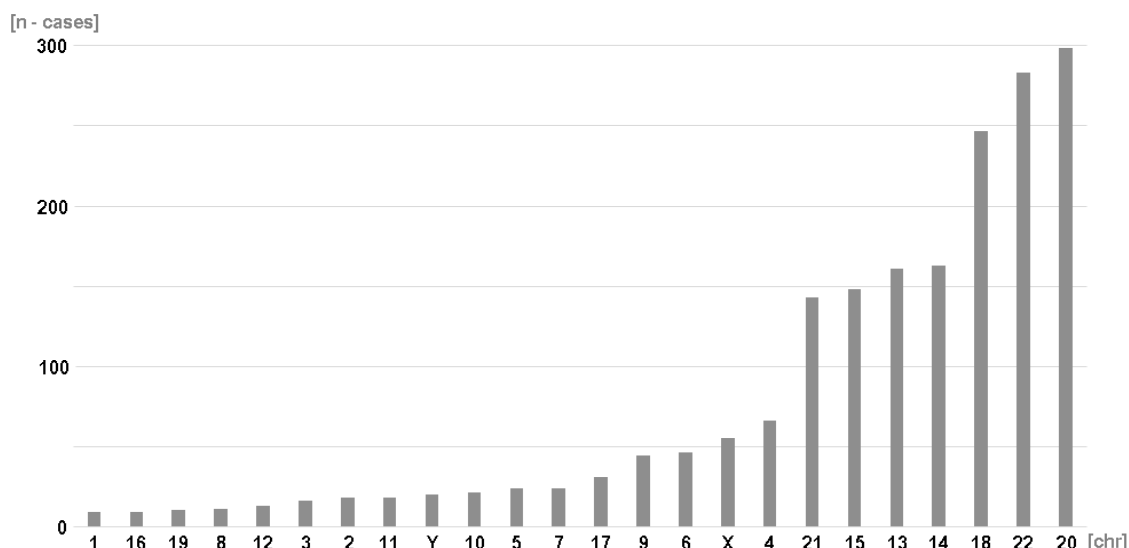


Figure 1 Frequency of reported RC cases per chromosome (chr) and sorted by number of reports (n).

In Figure 2, the overall 148/1879 cases (7.9%) without or with minor clinical signs are presented chromosome-wise, compared to the 92.1% of cases that have major clinical problems due to RC presence. Interestingly, for chromosomes 7, 12, 16, 19, 21 and Y between 20 and 60% of the RC-carriers have no or only minor clinical signs (including infertility as reason for diagnostics).



Figure 2 The reported RC cases per chromosome (chr) are set as 100%, each. Highlighted in green are those cases with no or minor clinical signs, compared to those with (significant) clinical signs and symptoms (red).

In Table 2, susceptibilities of RC-patients for aneuploidy and microdeletion syndromes as well as cancer susceptibility are summarized, based on the data from [18].

Table 2 Susceptibilities of RC-patients for aneuploidy and microdeletion syndromes as well as cancer.

Chromosome	Aneuploidy syndrome	Microdeletion syndrome	Cancer susceptibility
1	n.a.	1p36.3 syndrome	leukemia, lymphoma, solid tumor
4	n.a.	Wolf-Hirschhorn syndrome (WHS)	Not seen yet
5	n.a.	Cri du Chat syndrome	Not seen yet
7	n.a.	n.a.	skin cancer
9	n.a.	9p subtelomere deletion syndrome 9q subtelomere deletion syndrome	Not seen yet
11	n.a.	n.a.	Wilms tumor
13	Patau syndrome	n.a.	Retinoblastoma
15	n.a.	Prader-Willi-syndrome Angelman-syndrome	Not seen yet
17	n.a.	Miller-Diecker syndrome (MDS)	Neurofibromatosis type 1
18	Edwards syndrome	n.a.	n.a.
21	Down syndrome	n.a.	leukemia
22	n.a.	Phelan-McDermid syndrome	Neurofibromatosis type 2/ teratoid rhabdoid tumor
X	Turner syndrome Klinefelter syndrome	n.a.	n.a.
Y	Turner syndrome Klinefelter syndrome	n.a.	n.a.

4. Discussion

RCs pose a diagnostic dilemma, especially when an RC is detected prenatally. Genotype-phenotype correlations are challenging, if not impossible, as tissue-specific mosaicism appears to influence clinical outcomes significantly.

The case collection of all published RCs provides a comprehensive overview of yet published cases. As it also includes data on the clinical consequences of the RCs, for the first time, it could be shown that ~8% of RC carriers are less affected than expected. The data indicating that this percentage varies between 0 and 60%, according to the RC's chromosomal origin, is new and may also aid in genetic counseling.

Furthermore, it is clear from previous studies [1, 2, 17] and summarized in the database presented here [18], that known critical regions of microdeletion syndromes influence the clinical

outcome, RCs can enhance the risk for an aneuploidy syndrome and that specific cancer susceptibilities can be induced by RC-presence (Table 2). This offers solid potential clinical value for the database in prenatal counseling or the interpretation of variants.

Nevertheless, a potential bias in RC reports in the literature must be considered. The following may be present:

- an underrepresentation of mild or asymptomatic RC cases that were not included in the diagnosis at all;
- a geographical bias in the literature for inclusion of cases in the database, as articles might have only been published in local languages; and
- different diagnostic methods across decades and countries, which could lead, for example, to misdiagnosis of RCs as simple terminal deletions if no chromosome analysis was performed after a chromosome microarray.

Future studies can be based on the data included in the RC database. They may lead to innovative ideas on how mosaicism and gene copy numbers influence clinical outcomes in individual cases.

Author Contributions

Conceptualization, T.L. P.L.; methodology, T.L and P.L.; software, T.L.; validation, T.L., and P.L.; resources, T.L.; data curation, T.L.; writing—original draft preparation, T.L.; writing, review and editing, T.L. and P.L.; visualization, T.L.; supervision, T.L.; project administration, T.L. All authors have read and agreed to the published version of the manuscript.

Competing Interests

The authors have declared that no competing interests exist.

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