Check for updates

RESEARCH NOTE

Rheumatoid arthritis in an adult patient with mosaic distal 18q-, 18p- and dicentric ring chromosome 18 [version 1; peer review: 2 approved with reservations]

Alanna Chau¹, KH Ramesh², Anand D Jagannath³, Shitij Arora ³

¹Albert Einstein College of Medicine, Bronx, New York City, NY, USA

²Department of Pathology, Montefiore Medical Center, Bronx, New York City, NY, USA

³Department of Medicine, Montefiore Medical Center, Bronx, New York City, NY, USA

V1 First published: 02 Nov 2017, 6:1940
<https://doi.org/10.12688/f1000research.11539.1>

Latest published: 28 Feb 2018, 6:1940
<https://doi.org/10.12688/f1000research.11539.2>

Abstract

Ring chromosome 18 has a highly variable phenotype, depending on the extent of distal arm deletions. It is most commonly presented as a combination of 18p- and distal 18q- syndrome. IgA deficiency and autoimmune diseases have been previously described in these patients. Seven cases of juvenile rheumatoid arthritis (JRA) have been reported. Here we report the first case of late onset rheumatoid arthritis (RA) in a 32 year old Dominican woman with hypothyroidism, vitiligo, IgA deficiency, interstitial lung disease (ILD), cystic bronchiectasis, and features consistent with 18p- and distal 18q syndrome. Comparative genome hybridization analysis showed a del(18p11.21p11.32), dup(18q11.21-q22.1), and del(18q22.1-q23). Chromosomal analysis and fluorescence in situ hybridization showed three cell lines. One cell line was detected with a dicentric ring chromosome, another with duplication of the long arm and no short arm, and lastly a long arm terminal deletion of 18. The multiple autoimmune findings in our patient lends further support to the idea of loci on chromosome 18 playing a role in autoimmune disease expression. Late onset RA and ILD in a patient with chromosome 18 abnormalities are novel findings and are additional conditions to be aware of in this population.

Keywords

ring chromosome 18, rheumatoid arthritis, interstitial lung disease

Open Peer Review

Approval Status

	1	2
version 2		
(revision)
28 Feb 2018	view	view

version 1
02 Nov 2017	view	view

1. **György Kosztolányi**, University of Pécs, Pécs, Hungary

2. **Jannine D. Cody** , University of Texas Health Science Center at San Antonio, San Antonio, USA

Any reports and responses or comments on the article can be found at the end of the article.

Corresponding author: Shitij Arora (drshitij@yahoo.com)

Competing interests: No competing interests were disclosed.

Grant information: The author(s) declared that no grants were involved in supporting this work.

Copyright: © 2017 Chau A *et al.* This is an open access article distributed under the terms of the [Creative Commons Attribution License](#), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

How to cite this article: Chau A, Ramesh K, Jagannath AD and Arora S. **Rheumatoid arthritis in an adult patient with mosaic distal 18q-, 18p- and dicentric ring chromosome 18 [version 1; peer review: 2 approved with reservations]** F1000Research 2017, 6:1940 <https://doi.org/10.12688/f1000research.11539.1>

First published: 02 Nov 2017, 6:1940 <https://doi.org/10.12688/f1000research.11539.1>

Introduction

Changes in the structure of chromosome 18 are implicated in a number of conditions affecting health and development. 18p- and distal 18q- syndrome has been estimated to occur in 1/50,000 and 1/40,000 live births, respectively. The characteristics of 18p- syndrome are wide ranging and include speech delay, holoprosencephaly spectrum, micrognathia, ptosis, flat nasal bridge, wide mouth with short upper lip, excessive dental caries, large protruding ears, and skeletal abnormalities. 18q- syndrome also presents with a wide variety of clinical features that commonly includes foot anomalies, carp like mouth, midface hypoplasia, cleft palate, cleft lip, inner epicanthal folds, slanted palpebral fissures, narrow or atretic external auditory canals and low set ears. Features common to both syndromes include intellectual disability, short stature, microcephaly, tone abnormalities, seizures, hearing loss and cardiac defects. The phenotypic severity of either condition appears to be correlated with the amount of genetic material affected¹.

Ring chromosome 18, or r(18), is a rarer condition that most commonly forms when there is breakage in both chromosome arms, fusion of those breakpoints and the subsequent loss of the distal fragments². Ring chromosomes can also result from terminal deletions as well as contiguous duplication, with some of these cases demonstrating inversion of these duplications and thus an inv dup del rearrangement mechanism. As a result of the inconsistent amount of duplication and hemizyosity of the distal ends, the r(18) phenotype is extremely variable. Clinical characteristics are typically a combination of 18p- and distal 18q- syndrome³.

IgA deficiency and immunological diseases such as type 1 diabetes mellitus (T1DM), juvenile rheumatoid arthritis (JRA), Grave's disease, hypothyroidism, and vitiligo have been reported in a number of individuals with 18p-, 18q-, and to a lesser extent r(18)³⁻⁸. These numerous reports may represent chance relationships or suggest true genetic linkages. To the best of our knowledge, there have been seven reported cases of chromosome 18 abnormalities and JRA (see [Table 1](#)). Here we report the first case of late onset rheumatoid arthritis (RA) associated with mosaic 18p-, distal 18q-, and r(18) in a 32 year old Dominican woman with intellectual disability, hypothyroidism, vitiligo, IgA deficiency, interstitial lung disease (ILD), cystic bronchiectasis, and features consistent with both 18p- and distal 18q- syndrome.

Case report

Patient information

The patient was a 32-year-old Dominican woman who presented to the emergency room with fever, hypoxia, wheezing, shortness of breath, cough productive of yellow sputum, and coarse breath sounds. She was hospitalized three months prior for community acquired pneumonia. She was subsequently admitted to the general medicine service for management of presumed healthcare associated pneumonia.

She immigrated with her family to the US from the Dominican Republic 2 years ago. Unfortunately, we have no access to previous medical records and past medical history was obtained

from her mother. The patient is the second child of a healthy non-consanguineous couple. At the time of birth, mother and father were 25 and 30 years old, respectively. Prenatal ultrasound was not done. She was born full term with birth weight of 2948 g. At birth, the patient was found to have an abnormal head shape, enlarged heart and heart murmur that resolved by 4 years after taking an unspecified oral medication. Cleft palate and left clubfoot were surgically repaired at age 3 and 4 years, respectively. Dentition was initially normal, however teeth fell early or had extensive caries. At age 9 years skin and hair depigmentation began and she was diagnosed with vitiligo. She is hypothyroid and maintained on levothyroxine. At age 18 years monthly menses began. Over the years hearing has deteriorated, necessitating louder cues to respond. At age 19 years she began to develop morning pain and swelling in her knees. Symptoms progressed to left shoulder, bilateral wrists, proximal interphalangeal and metacarpophalangeal joints. At age 31 years she was diagnosed with rheumatoid arthritis (RA) by the rheumatology service. At presentation she was on prednisone 5mg daily, methotrexate 17.5mg weekly, status post 2 doses of adalimumab 40mg every 2 weeks. Acetaminophen and diclofenac used as needed. She was previously also on sulfasalazine 1000mg twice daily but was discontinued due to aggressiveness. She was diagnosed with mild intermittent asthma in the past year.

She began to walk at age 4 years. She never attended school, has a vocabulary of 10–12 words, follows basic commands, independently feeds, dresses, and bathes herself. She has a 37 year old brother with mild learning disability; he completed school, works and lives independently. There was no family history of similar congenital defects or autoimmune disorders.

On physical examination, her height was 135 cm and weight was 53 kg. Head was microcephalic with circumference of 51 cm. She was nonverbal and appears to fall under severe-profound intellectual disability. Skin, head and body hair was hypopigmented with a few patches of pigmentation and a large 2x1 cm left neck nevus. Midface is hypoplastic. Eyes were symmetrical with a left limbal dermoid cyst. Mouth was carp like with downturned corners. Residual posterior cleft palate and split uvula were present. Dentition was poor with several teeth broken, missing, or carious. No murmurs were appreciated. On lung exam, bilateral basilar crackles and scattered wheezes were appreciated. There was full range of motion in limbs and normal muscle tone. There was mild tenderness in left shoulder. Surgically corrected left foot noted.

Laboratory results showed positive antinuclear antibody (ANA) at a titer of <1:40, positive rheumatoid factor (RF) at 81.1 IU/mL, negative anti-citrullinated cyclic protein (anti-CCP) at 16AU, elevated erythrocyte sedimentation rate at 42 mm/hr and C-reactive protein at 1.3 mg/dL. Quantitative immunoarray revealed IgA deficiency at 88.5mg/dL, normal IgM and IgG.

Radiographic evaluation revealed osteopenia of left foot, ankle, hands and wrists. Images of knees revealed small left and trace right joint effusion. Transthoracic echocardiogram showed moderate tricuspid valve regurgitation and moderate pulmonary hypertension.

Table 1. Clinical comparisons between previously reported chromosome 18 abnormalities, and our case.

Authors	Syndrome	Sex	Age of onset	Joint involvement	Extra-articular manifestations	Lab studies	Other immunological and endocrine problems	Major abnormalities	Developmental problems
Finley <i>et al.</i> ⁶ (1972)	18p-	F	9 months	Pain/swelling in wrists, R knee, R ankle; contractures in elbows, knees, hips	Fever, rash, hepatosplenomegaly	+ANA	-	Short stature, hypertelorism, epicanthal folds, flat nasal ridge, short fifth finger, elevated triradius	Mild MR, delayed speech
Petty <i>et al.</i> ⁷ (1987)	r(18)	M	11 years	Pain/swelling in knees, ankles; contractures and effusions in knees X-ray: wnl	-	- ANA + RF	IgA deficiency	Tetralogy of Fallot, microcephaly, short stature, midface dysplasia, nystagmus, malabsorption	Severe MR
	Interstitial 18q- **	F	5.5 years	Pain/swelling in knees, R wrist, ankles; effusions in knees X-ray: wnl	Erythematous macules, urticaria	- ANA - RF	Reduced IgG and IgM	Short stature, hypertelorism, flat nasal bridge, broad palate, bifid uvula, external auditory canal atresia, large mouth, unilateral simian crease, short/broad hands	Moderate MR
Hansen <i>et al.</i> (1994) ⁸	Distal 18q-	M	4 years	Pain/swelling in knees, L ankle; effusions in knees; contracture L knee; XR: TMJ arthritic changes, L knee subchondral erosions, L patella enlargement	Uveitis	+ANA - RF	Elevated IgG and IgM	Hypopspadias, umbilical hernia, cleft left palate, hypertelorism, atretic ear canals, severe hearing loss, hypotonia, joint hypermobility, syndactylia of second and third toes	Normal IQ range with learning difficulty, delayed speech, attention, visual-spatial orienting, fine and gross motor skill difficulties
Czakó <i>et al.</i> (2002) ¹⁰	Translocation: 18p-, 20p trisomy	F	6 years	Large joints, small finger joints	-	+ESR +CRP + Waaler Rose test	Milk protein intolerance	Oval flat face, upslanting palpebral fissures, periorbital fullness, hypoplastic midface, flat nose, down turned corners of mouth, muscular hypotonia	Severe psychomotor retardation

Authors	Syndrome	Sex	Age of onset	Joint involvement	Extra-articular manifestations	Lab studies	Other immunological and endocrine problems	Major abnormalities	Developmental problems
Rosen <i>et al.</i> (2004) ⁵	Distal 18q-	F	8 years	Pain/swelling, effusions in knees, R SCJ X-ray: knee effusions MRI: R SCJ synovitis	-	+ ANA - RF DRB*11 allele	Elevated IgG	ASD, short stature, left aural atresia, right external auditory canal atresia, prominent nasal pyramids, hypoplastic alae nasi, broad mouth, thin upper lip, short philtrum, joint hypermobility	Normal IQ range with learning difficulty
Recacalti <i>et al.</i> ⁴ (2010)	18p-	F	<5 years?	?	?	?	-	Seizures, microcephaly, midline anomaly (ectopic neurohypophysis) growth retardation, blue sclera, sparse hair, upslanting palpebral fissures, epicanthal folds, high arched palate, low set, ears, micrognathia, retrognathia, excessive caries, cupid bow lips, long philtrum, short neck, short and broad hallux, sacral dimple, hypotonia	MR, speech delay, psychomotor retardation
Our case	r(18)	F	19 years	Pain/swelling in L shoulder, knees, wrists, hands X-ray: knee effusions; osteopenia in L foot, ankle, hands, wrists	ILD?	+ ANA + RF - CCP + ESR + CRP	IgA deficiency, hypothyroidism, vitiligo	Short stature, microcephaly, cleft palate, bifid uvula, midface hypoplasia, carp-like mouth, excessive dental caries, hearing loss, club foot	Severe MR

+ = present, - = absent, ? = not reported; F = female, M = male, R = right, L = left; ANA = antinuclear antibodies, RF = rheumatoid factor, CCP = cyclic citrullinate peptide; ASD = atrial septal defect, IQ = intelligence quotient, MR = mental retardation ** Possible drug related etiology, occurred after trimethoprim sulfamethoxazole use with intermittent recurrences

During this admission, high resolution CT chest showed scattered areas of cystic bronchiectasis and bilateral right upper lobe predominant ground glass opacities. She was subsequently treated for bronchiectasis exacerbation with zosyn for a total of 7 days. She improved clinically and was discharged with extensive follow up appointments.

Cytogenetics

Her primary care physician referred her to the genetics department in our hospital for suspected chromosomal abnormalities. Comparative genome hybridization (aCGH) was done using the custom designed Agilent 44,000 oligonucleotide probes microarray. Probes were placed approximately every 50–100 kb across the entire euchromatic genome with a resolution of 500 kb. The

probe density at clinically relevant regions was about 5–10 kb, thus increasing the resolution to 50 kb in targeted regions based on hg19. The aCGH revealed a 14 Mb deletion at 18p11.21-p11.32 (148963-14188180)x1, a 47.8Mb duplication at 18q11.21-q22.1 (18542074-66367715)x3, and a 11.6 Mb deletion at 18q22.1-q23 (66377285-78010032)x1 (Figure 1a). Standard chromosomal analysis and fluorescence in situ hybridization (FISH) revealed a mosaic condition. One cell line contained a dicentric ring chromosome. Another cell line showed duplication of the long arm and no short arm, 46XX, r(18)(q11.3q23) (Figure 1b–c). A third cell line was detected with terminal long arm deletion, 46XX del(18)(q22). Her mother had a normal analysis performed with her consent, alongside the patients' analysis. The paternal sample was not available.

Figure 1. A. CGH panel illustrates deletions on distal arms (red) and duplication of proximal long arm (blue). B. Karyotype in metaphase showing a ringed chromosome 18. C. FISH analysis showing a ringed chromosome 18.

Discussion

The described chromosomal abnormalities are most likely *de novo*, since maternal analysis was normal and her father was normal in appearance and health. Furthermore, ring chromosomes usually arise *de novo*, with only 1% inherited⁹. Of the inherited cases, 90% are maternal since the presence of a ring blocks spermatogenesis and induces infertility in males.

Consistent with previously reported cases of r(18) (see Table 1), our patient had many of the characteristics associated with both 18p- and distal 18q- syndrome. The features shared between the two conditions include intellectual disability, short stature, microcephaly, IgA deficiency, autoimmune disorders (RA, vitiligo, hypothyroidism), and likely conductive hearing loss. Features specific to 18p- include excessive dental caries, while those specific to distal 18q- include cleft palate, carp shaped mouth, and clubfoot. Duplication did not appear to cause any distinguishing Edwards syndrome manifestations such as clenched fist, rocker bottom feet, severe organ involvement, and failure to thrive.

The unique feature of our patient was her late onset of RA compared to the early JRA previously reported^{4-8,10}. Our patient was RF positive, anti-CCP negative and met 9/10 of the 2010 American College of Rheumatology (ACR) Clinical Classification Criteria for RA⁶. To the best of our knowledge there have been seven reported, and six published, cases of RA associated with chromosome 18 abnormalities (Table 1). Daentl first mentioned an unpublished case of JRA in a patient with 18p- and IgA deficiency⁷. In the first published case, Finley *et al.* reported a 9-month-old female with 18p-, swelling and contractures in many joints, fever, rash, and hepatosplenomegaly, consistent with JRA⁶. JRA has subsequently been associated with cases of 18q- as well^{3,7,9}.

The exact genes involved with RA and autoimmune disease development in chromosome 18 abnormalities are still not well defined. There is a suggested link between PTPN2 (protein tyrosine phosphatase non-receptor type 2), located at 18p11.2-11.3, and RA and T1DM^{11,12}. Genome wide studies have shown evidence for the association of the PTPN2 locus with RA susceptibility in both Japanese and European populations^{11,13}. A case similar to ours was reported by Jain *et al.* with *de novo* r(18), del(18q23-18qter) and del(18p11.3-18pter) associated with hyperthyroidism, T1DM, vitiligo, and IgA deficiency, but not RA³. Their case had a more distal deletion that likely spared PTPN2. Another autoimmune critical region was proposed on 18p, with molecular breakpoints at 12,316,423-1,231,7830; interestingly, PTPN2 is not in this region¹². The genetic basis of autoimmune disease is not as well established in 18q- compared to 18p-. On the long arm, Merriman *et al.* proposed a locus at 18q12-21 that influences development of autoimmune diseases¹⁴. Another gene of interest is NFATc1 (nuclear factor of activated T cells) at 18q23, implicated in maintaining the programmed death receptor (PD-1) and ligand (PD-L) pathway that is essential for regulatory T cells to terminate immune responses and protect against autoimmunity^{15,16}. It is difficult to establish a definitive genotype-phenotype association, but it appears plausible that this proposed autoimmune critical region and PTPN2 on the short arm, as well as NFATc1 on the long arm may play a part in the autoimmune diseases seen in our patient.

Overall, adult RA has a poorer outcome compared to JRA¹⁷. Mortality rates in RA patients are increased due to medication related infections, gastrointestinal bleeding as well as extra-articular pulmonary, renal disease, and cardiovascular manifestations¹⁷. Our patient was also found to have ILD, bronchiectasis, and pulmonary hypertension. To the best of our knowledge, there is no known connection between interstitial lung pathologies and chromosome 18 abnormalities. However, ILD and bronchiectasis are known extra-articular manifestations of RA. In a population study, the lifetime risk of developing ILD was 7.7% for RA patients and 0.9% for non-RA subjects¹⁸. The classic presentation is a reticular, reticulonodular or honeycomb pattern in the lung bases.

The patient was also on several medications known to cause drug-induced interstitial lung disease (DI-ILD) including: methotrexate, adalimumab, sulfasalazine, and diclofenac¹⁹. The predominantly bilateral patchy ground-glass opacities with upper lobe predominance in our patient do suggest a hypersensitivity pneumonitis picture. Unfortunately, ground-glass opacities are non-specific and pattern of involvement on HRCT does not always correspond to histological findings. Medications known to cause DI-ILD were discontinued in our patient, with further management focusing on better characterizing the extent and etiology of ILD and continuation of steroid therapy.

Our report describes the first case of late onset RA associated with mosaic 18p-, 18q- and dicentric r(18). The complex rearrangements were detected by aCGH, karyotype and FISH. Her syndrome has features of both 18q- and 18p-, including multiple autoimmune disorders that support the idea of genetic loci on chromosome 18 playing a role in disease expression. Additionally, the finding of ILD - whether caused by RA, drug exposure, or an unexplored linkage - is an important condition to be aware of in patients with chromosome 18 abnormalities and autoimmune diseases. Ultimately, further studies are required to better define the genotype-phenotype associations that will further the clinical management of these patients.

Consent

Written and informed consent was obtained from the mother, who was the designated health care proxy prior to publishing this case report, for publication of any potentially identifiable clinical data that may be associated.

Author contributions

AC wrote the manuscript. KR contributed with the cytogenetics analysis. AJ and SA were involved in the care of this patient. AC and SA conceptualized the manuscript.

Competing interests

No competing interests were disclosed.

Grant information

The author(s) declared that no grants were involved in supporting this work.

Acknowledgements

We would like to thank the patient and her family for their participation.

References

1. Kline AD, White ME, Wapner R, *et al.*: **Molecular analysis of the 18q- syndrome- and correlation with phenotype.** *Am J Hum Genet.* 1993; **52**(5): 895–906.
[PubMed Abstract](#) | [Free Full Text](#)
2. Guilherme RS, Meloni VF, Kim CA, *et al.*: **Mechanisms of ring chromosome formation, ring instability and clinical consequences.** *BMC Med Genet.* 2011; **12**: 171.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
3. Jain N, Reitnauer PJ, Rao KW, *et al.*: **Autoimmune polyendocrinopathy associated with ring chromosome 18.** *J Pediatr Endocrinol Metab.* 2011; **24**(9–10): 847–50.
[PubMed Abstract](#) | [Publisher Full Text](#)
4. Recalcati MP, Valtorta E, Romitti L, *et al.*: **Characterisation of complex chromosome 18p rearrangements in two syndromic patients with immunological deficits.** *Eur J Med Genet.* 2010; **53**(4): 186–91.
[PubMed Abstract](#) | [Publisher Full Text](#)
5. Rosen P, Hopkin RJ, Glass DN, *et al.*: **Another patient with chromosome 18 deletion syndrome and juvenile rheumatoid arthritis.** *J Rheumatol.* 2004; **31**(5): 998–1000.
[PubMed Abstract](#)
6. Finley SC, Finley WH, Johnson JC, *et al.*: **Rheumatoid arthritis in the 46, XX, 18p- syndrome.** *Clin Genet.* 1972; **3**(6): 465–9.
[PubMed Abstract](#) | [Publisher Full Text](#)
7. Petty RE, Malleson P, Kalousek DK: **Chronic arthritis in two children with partial deletion of chromosome 18.** *J Rheumatol.* 1987; **14**(3): 586–7.
[PubMed Abstract](#)
8. Hansen US, Herlin T: **Chronic Arthritis in a Boy with 18q- Syndrome.** *J Rheumatol.* 1994; **21**(10): 1958–9.
[PubMed Abstract](#)
9. Caba L, Rusu C, Plăiașu V 5th, *et al.*: **Ring autosomes: some unexpected findings.** *Balkan J Med Genet.* 2012; **15**(2): 35–46.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
10. Czakó M, Riegel M, Morava É, *et al.*: **Patient with rheumatoid arthritis and MCA/MR syndrome due to unbalanced der(18) transmission of a paternal translocation t(18;20)(p11.1;p11.1).** *Am J Med Genet.* 2002; **108**(3): 226–8.
[PubMed Abstract](#) | [Publisher Full Text](#)
11. Cobb JE, Plant D, Flynn E, *et al.*: **Identification of the Tyrosine-Protein Phosphatase Non-Receptor Type 2 as a Rheumatoid Arthritis Susceptibility Locus in Europeans.** *PLoS One.* 2013; **8**(6): e66456.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
12. Hasi-Zogaj M, Sebold C, Heard P, *et al.*: **A review of 18p deletions.** *Am J Med Genet C Semin Med Genet.* 2015; **169**(3): 251–64.
[PubMed Abstract](#) | [Publisher Full Text](#)
13. Okada Y, Terao C, Ikari K, *et al.*: **Meta-analysis identifies nine new loci associated with rheumatoid arthritis in the Japanese population.** *Nat Genet.* 2012; **44**(5): 511–6.
[PubMed Abstract](#) | [Publisher Full Text](#)
14. Merriman TR, Cordell HJ, Eaves IA, *et al.*: **Suggestive Evidence for Association of Human Chromosome 18q12-q21 and Its Orthologue on Rat and Mouse Chromosome 18 With Several Autoimmune Diseases.** *Diabetes.* 2001; **50**(1): 184–94.
[PubMed Abstract](#) | [Publisher Full Text](#)
15. Cody JD, Sebold C, Heard P, *et al.*: **Consequences of chromosome18q deletions.** *Am J Med Genet C Semin Med Genet.* 2015; **169**(3): 265–80.
[PubMed Abstract](#) | [Publisher Full Text](#)
16. Francisco LM, Sage PT, Sharpe AH: **The PD-1 pathway in tolerance and autoimmunity.** *Immunol Rev.* 2010; **236**(1): 219–42.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
17. Prahalad S, Glass DN: **Is juvenile rheumatoid arthritis/juvenile idiopathic arthritis different from rheumatoid arthritis?** *Arthritis Res.* 2002; **4**(Suppl 3): 303–10.
[Publisher Full Text](#) | [Free Full Text](#)
18. Bongartz T, Nannini C, Medina-Velasquez YF, *et al.*: **Incidence and mortality of interstitial lung disease in rheumatoid arthritis: A population-based study.** *Arthritis Rheum.* 2010; **62**(6): 1583–91.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
19. Schwaiblmair M, Behr W, Haeckel T, *et al.*: **Drug Induced Interstitial Lung Disease.** *Open Respir Med J.* 2012; **6**: 63–74.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)

Open Peer Review

Current Peer Review Status: ? ?

Version 1

Reviewer Report 27 November 2017

<https://doi.org/10.5256/f1000research.12465.r27903>

© 2017 Cody J. This is an open access peer review report distributed under the terms of the [Creative Commons Attribution License](#), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Jannine D. Cody

Department of Pediatrics, University of Texas Health Science Center at San Antonio, San Antonio, TX, USA

This manuscript describes a single 32 year old woman with Ring 18 and rheumatoid arthritis. Overall the manuscript is well written, however there are several items that need further work before publication.

1. Most of the literature on Ring 18 has been omitted. The paper would benefit from a better review of Ring 18 as opposed to mostly 18p- and 18q-. Has the lung disease ever been reported?
2. The methods and data that determined the actual chromosome content are missing. The percent that each cell type is present in the blood as well as the FISH studies definitively demonstrating each should be included. From the text it is not clear if the "duplication of the long arm" is present as a ring or an isochromosome. The aCGH showing net copy number suggests that not all of the long arm is duplicated since a larger proportion of cells have an 18q terminal deletion than have an 18p terminal deletion. What percent of the cells actually have a ring chromosome?
3. The interpretation of the FISH data needs to be described more fully. Why are there two BCL2 probes? I don't see a D18Z1 signal?
4. The table needs to be made more clear in its title that it only includes RA cases and not all Ring 18 or 18q-, 18p- cases (at least I think that is the intent).
5. In the first paragraph of the discussion, the last sentence needs a reference.

Is the work clearly and accurately presented and does it cite the current literature?

Partly

Is the study design appropriate and is the work technically sound?

Yes

Are sufficient details of methods and analysis provided to allow replication by others?

No

If applicable, is the statistical analysis and its interpretation appropriate?

Not applicable

Are all the source data underlying the results available to ensure full reproducibility?

No source data required

Are the conclusions drawn adequately supported by the results?

Partly

Competing Interests: No competing interests were disclosed.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Reviewer Report 23 November 2017

<https://doi.org/10.5256/f1000research.12465.r27904>

© 2017 Kosztolányi G. This is an open access peer review report distributed under the terms of the [Creative Commons Attribution License](#), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

György Kosztolányi

Department of Medical Genetics, Clinical Center, University of Pécs, Pécs, Hungary

This is a well documented case report which may contribute to our knowledge on the clinical consequences of chromosome 18 abnormalities. I suggest to accept the MS for publication on condition that the authors consider a major and some minor remarks for modification.

Major remark

The routine cytogenetics description is too short. Nothing is written about the percentages of the "mosaic cell lines" (as the authors write), although one of the unique characteristics of ring chromosomes is their dynamic nature. As a result of mitotic difficulties, a ring chromosome is subject of additional cytogenetic mutations, resulting in continuous generation of secondary aneuploidy cells. Accordingly, this dynamic mutations series may manifest themselves as "mosaic cell lines", however, the survival of such cells as cell line, as well as the explanation of their presence being "cell lines" is questionable. I would recommend to refer to this widely accepted explanation for the presence of differentially shaped chromosomes in patients with ring chromosome, at least as an alternativ possibility. (e.g. Kosztolányi G: Does "ring syndrome" exist?

Hum.Genet. 1987; 75:174-179)

Minor remark

Some peculiarity of the case should be highlighted with more emphasis. E.g., Detecting a chromosome abnormality in a patient at the age of 32 is rare – it should be highlighted in the paper. Also the extreme severity of the somatic and mental underdevelopment should be pointed on abstract.

Is the work clearly and accurately presented and does it cite the current literature?

Partly

Is the study design appropriate and is the work technically sound?

Yes

Are sufficient details of methods and analysis provided to allow replication by others?

Yes

If applicable, is the statistical analysis and its interpretation appropriate?

Not applicable

Are all the source data underlying the results available to ensure full reproducibility?

No source data required

Are the conclusions drawn adequately supported by the results?

Yes

Competing Interests: No competing interests were disclosed.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

The benefits of publishing with F1000Research:

- Your article is published within days, with no editorial bias
- You can publish traditional articles, null/negative results, case reports, data notes and more
- The peer review process is transparent and collaborative
- Your article is indexed in PubMed after passing peer review
- Dedicated customer support at every stage

For pre-submission enquiries, contact research@f1000.com

F1000Research