



LUND UNIVERSITY

Constitutional and somatic deletions of the Williams-Beuren syndrome critical region in Non-Hodgkin Lymphoma

Guenat, David; Quentin, Samuel; Rizzari, Carmelo; Lundin, Catarina; Coliva, Tiziana; Edery, Patrick; Fryssira, Helen; Bermont, Laurent; Ferrand, Christophe; Soulier, Jean; Borg, Christophe; Rohrlich, Pierre-Simon

Published in:

Journal of Hematology & Oncology

DOI:

[10.1186/s13045-014-0082-4](https://doi.org/10.1186/s13045-014-0082-4)

2014

[Link to publication](#)

Citation for published version (APA):

Guenat, D., Quentin, S., Rizzari, C., Lundin, C., Coliva, T., Edery, P., Fryssira, H., Bermont, L., Ferrand, C., Soulier, J., Borg, C., & Rohrlich, P.-S. (2014). Constitutional and somatic deletions of the Williams-Beuren syndrome critical region in Non-Hodgkin Lymphoma. *Journal of Hematology & Oncology*, 7, Article 82. <https://doi.org/10.1186/s13045-014-0082-4>

Total number of authors:

12

General rights

Unless other specific re-use rights are stated the following general rights apply:

Copyright and moral rights for the publications made accessible in the public portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognise and abide by the legal requirements associated with these rights.

- Users may download and print one copy of any publication from the public portal for the purpose of private study or research.
- You may not further distribute the material or use it for any profit-making activity or commercial gain
- You may freely distribute the URL identifying the publication in the public portal

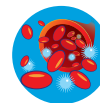
Read more about Creative commons licenses: <https://creativecommons.org/licenses/>

Take down policy

If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

LUND UNIVERSITY

PO Box 117
221 00 Lund
+46 46-222 00 00



LETTER TO THE EDITOR

Open Access

Constitutional and somatic deletions of the Williams-Beuren syndrome critical region in Non-Hodgkin Lymphoma

David Guenat^{1,2*}, Samuel Quentin³, Carmelo Rizzari⁴, Catarina Lundin⁵, Tiziana Coliva⁴, Patrick Ederly⁶, Helen Fryssira⁷, Laurent Bermont⁸, Christophe Ferrand², Jean Soulier³, Christophe Borg^{2,9} and Pierre-Simon Rohrllich^{2,10}

Abstract

Here, we report and investigate the genomic alterations of two novel cases of Non-Hodgkin Lymphoma (NHL) in children with Williams-Beuren syndrome (WBS), a multisystem disorder caused by 7q11.23 hemizygous deletion. Additionally, we report the case of a child with NHL and a somatic 7q11.23 deletion. Although the WBS critical region has not yet been identified as a susceptibility locus in NHL, it harbors a number of genes involved in DNA repair. The high proportion of pediatric NHL reported in WBS is intriguing. Therefore, the role of haploinsufficiency of genes located at 7q11.23 in lymphomagenesis deserves to be investigated.

Keywords: Williams-Beuren syndrome, Non-Hodgkin Lymphoma, 7q11.23, Cancer predisposition, DNA repair

Findings

Chromosomal disorders are common circumstances for the discovery of a genetic predisposition to cancer allowing identification and localization of new oncogenes. Williams-Beuren syndrome (WBS) is a multisystem disorder caused by 7q11.23 hemizygous microdeletion [1]. WBS is not currently considered as a risk factor for cancer. However, the low incidence of both WBS and pediatric NHL (Non-Hodgkin Lymphoma) might hamper our ability to identify any association between these rare diseases. An increased risk of NHL in WBS might have easily been underestimated until today. Furthermore, the number of pediatric cancer reported in WBS has reached 11 cases and, strikingly, 8 (73%) of them where NHL, mostly Burkitt lymphoma (Table 1). Here, we report 2 novel cases of NHL in children with WBS and the additional case of a non-WBS child with NHL and somatic 7q11.23 deletion (see case description in Additional file 1).

Since several different deletions account for the genotype of WBS, we first investigated germline and somatic structural variants in these latest 3 patients using array-based CGH (Figure 1). We confirmed the presence of a constitutional 7q11.23 deletion in WBS patients. No germline Copy Number Variation (CNV) was observed in patient 3. Intriguingly, the somatically acquired 7q11.23 deletion that occurred in lymphoma of patient 3 was similar to the classical germline deletion observed in WBS patients and there was no evidence of other rearrangements occurred in this tumor. Lymphoma cells of WBS patients exhibited CNV commonly found in B cell lymphoma excepting a subclonal deletion of approximately 10 Mb at the locus 2q33.1-q35 involving *IKZF2* in WBS patient 2. A recent study by Holmfeldt et al. demonstrated that this deletion was common in low-hypodiploid acute lymphoblastic leukemia [11] but this deletion had never been described in NHL. Then, next generation sequencing of the WBS region showed a germline homozygous variant in exon 25 of *ELN* (c.1741G > C, p.Gly581Arg, rs.17855988) in the 2 WBS patients. *ELN* encodes elastin, a constituent of elastic fibers. Many variants of *ELN* has been described and were associated to the severity of cardiovascular symptoms of WBS patients. No recurrent variant was observed in the

* Correspondence: david.guenat@univ-fcomte.fr

¹Laboratory of Cellular and Molecular Biology, University Hospital of Besançon, 1 Bd Fleming, Batiment Diaclone, Besançon, France

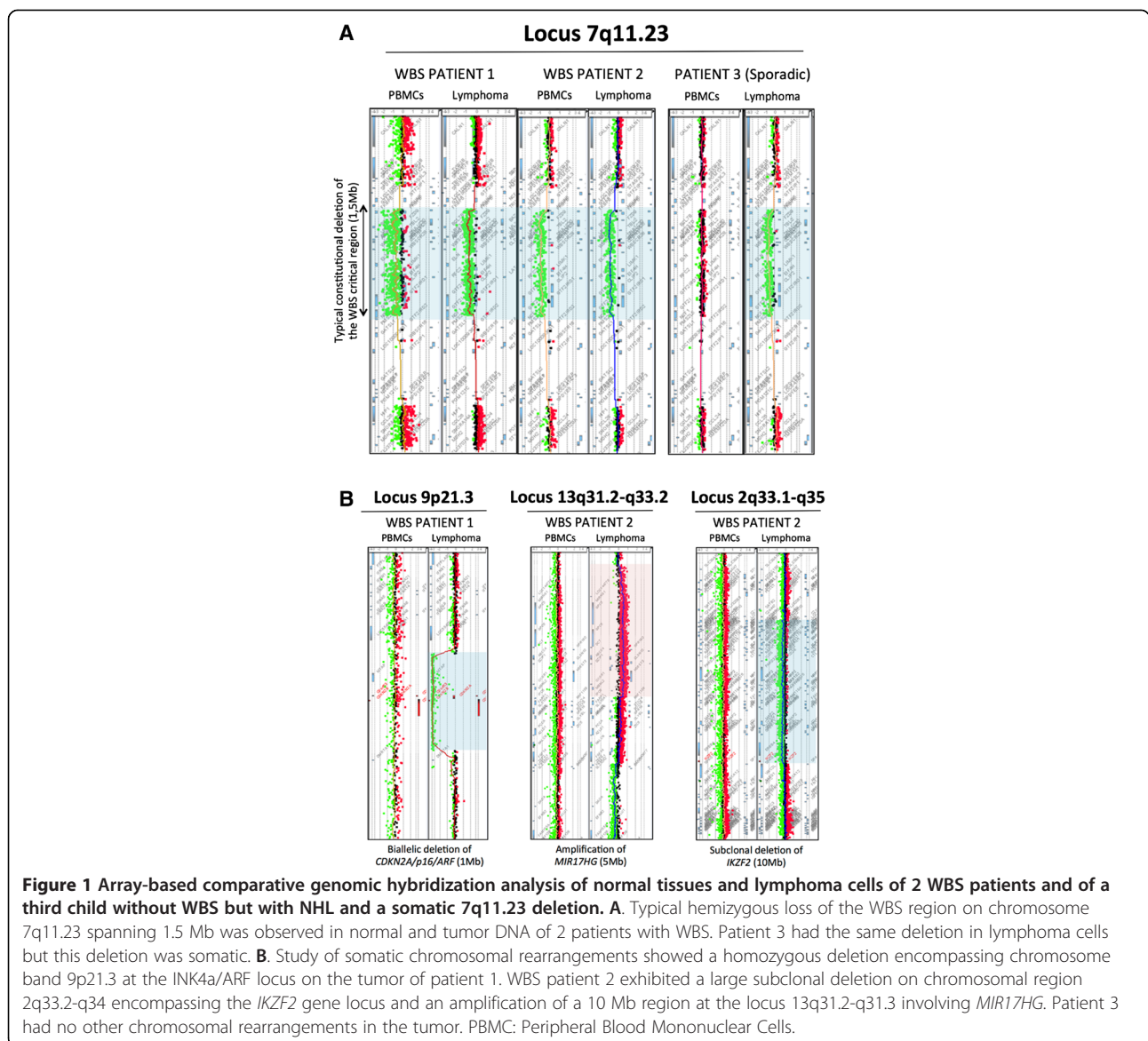
²UMR1098 Inserm/EFS-BFC/University of Franche-Comte, LabEx LipSTIC, Besançon, France

Full list of author information is available at the end of the article

Table 1 List of pediatric cancers reported in WBS patients

Study Samples	Authors	Date of publication	Age (years), gender	Type of tumor	Reference	
1	WBS Patient 1	Guenat D	TS	7, F	NHL (Burkitt)	-
2	WBS Patient 2	Guenat D	TS	10, M	NHL (B-NHL stage IV)	-
3	-	Vanhapiha N	2014	7, M	NHL (Burkitt) and Ewing sarcoma	[2]
4	-	Chonan M	2013	3, M	Astrocytoma	[3]
5	-	Zhukova N	2013	8, M	NHL (Burkitt)	[4]
6	-	Onimoe G	2011	10, F	NHL (Burkitt)	[5]
7	-	Urisarri Ruiz A	2008	12, M	NHL (T-cell)	[6]
8	-	Thornburg CD	2005	1,?	NHL (Burkitt)	[7]
9	-	Amenta S	2004	8, M	NHL (Burkitt)	[8]
10	-	Culic V	2002	14, M	ALL	[9]
11	-	Semmekrot BA	1985	5, ?	Astrocytoma	[10]

TS: This Study; NHL: Non-Hodgkin Lymphoma; ALL: Acute Lymphoblastic Leukemia, F: female; M: male.



27 other genes nor in the 2 miRNA loci of the WBS critical region.

A number of genes mapping to the WBS region are involved in DNA repair: 1) Eleven *PMS2* pseudogenes loci are located at 7q11.23. *PMS2* plays a crucial role in the DNA Mismatch Repair and a childhood cancer syndrome is associated to biallelic mutations of *PMS2* [12]. However, in our study the 3 patients showed stable microsatellites (Additional file 2); 2) *BAZ1B* encodes a transcription factor with an intrinsic tyrosine kinase domain that phosphorylates Tyr142 of histone H2A.X and is involved in the maintaining of gH2A.X in the sites of DNA damages [13]; 3) *RFC2* encodes a subunit of the Replication Factor C complex that interacts with BRCA1 for post replication repair after UV-induced DNA damage [14]; 4) *GTF2I* encodes a transcription factor that promotes DNA translesion synthesis and genomic stability interacting with PCNA and DNA polymerases [15]. Finally, the hypothesis of a constitutional genomic instability in WBS is consistent with the results of a study by Savina et al. that showed experimentally the relationship between an abnormal DNA-damage response and the 7q11.23 hemizygous microdeletion when comparing the comet assay data in FISH-positive and FISH-negative lymphocytes from WBS-suspected patients [16].

7q11.23 deletion has been found as a relatively common occurrence in pilocytic astrocytoma [17], of which variants have been reported in 2 patients with WBS [3,10]. Nevertheless, genome-wide copy number analysis in NHL, including a recent study by Conde et al. that analyzed 648 patients, ages 20 to 85 years, have not found a susceptibility locus at 7q11.23 [18]. However, NHL in adults encompasses a heterogeneous spectrum of diseases in which diffuse large B-cell lymphoma predominates. NHL in children is a more rare event and pediatric DLBCL is uncommon. Burkitt lymphoma that predominates in pediatric NHL, has also been studied by genome-wide CNV studies. Notably, Scholtysik et al. demonstrated a recurrent loss at 7q11.22, localized at the centromeric limit of the WBS critical region, in 39 cases of BL [19]. Amplifications of the WBS critical region have also been found in a variety of cancers including large B-cell lymphoma [20], ovarian adenocarcinoma [21], papillary thyroid carcinoma [22] and cholangiocarcinoma [23]. This might reflect complex mechanisms that regulate initiation/promotion of cancer cells by oncogenes and tumor suppressor genes clustered around recombination hot spots or fragile sites in the WBS region.

Although no epidemiological studies demonstrated an increased risk of cancer in WBS the high proportion of pediatric NHL reported in WBS and the occurrence of a somatic deletion of 7q11.23 in NHL is intriguing. In

these patients, NHL seems to arise in the presence of the typical WBS microdeletion and in the absence of homozygous mutation. The role of haploinsufficiency of genes located at 7q11.23 in lymphomagenesis deserves to be investigated.

Additional files

Additional file 1: Supplementary materials and methods [24].

Additional file 2: Study of microsatellites instability by capillary electrophoresis fragment analysis. All patients have stable microsatellites in both normal and tumor DNA when compared with the Microsatellite Instable positive control (Control MSI+). BL: Burkitt Lymphoma, PBMC: Peripheral Blood Mononuclear Cells.

Competing interests

The authors declare that they have no competing interests.

Authors' contribution

DG, JS, PSR and CB designed the study. SQ and JS performed CGH-array and analyzed the results. DG, and CF analyzed the next-generation sequencing data. LB performed Microsatellite instability assay. CR, TC, PSR, CL, HF and PE provided clinical and diagnostic input. DG, PSR, CL, CB and CR wrote the manuscript. All authors read, reviewed and approved the manuscript.

Acknowledgments

This work was funded by the French association "Cent pour sang la vie". We would like to acknowledge the study participants and their parents. We thank Brigitte Gilbert-Dussardier for her help in contacting the different investigators. We also thank "Comitato Maria Letizia Verga (Monza) per lo studio e la cura della leucemia infantile" for the continuous support to research activities of Carmelo Rizzari and Tiziana Coliva and "The Swedish Childhood Cancer Foundation" for financial support to research works of Catarina Lundin. Finally, we thank Annalisa Weygandt for the English language editing of the manuscript.

Author details

¹Laboratory of Cellular and Molecular Biology, University Hospital of Besançon, 1 Bd Fleming, Batiment Diaclone, Besançon, France. ²UMR1098 Inserm/EFS-BFC/University of Franche-Comte, LabEx LipSTIC, Besançon, France. ³Saint-Louis Hospital APHP and Hematology University Institute (IUH), University Paris-Diderot, Paris, France. ⁴Department of Pediatrics, San Gerardo Hospital, University of Milano-Bicocca, Monza, Italy. ⁵Department of Clinical Genetics, University and Regional Laboratories Region Skane, Lund University, Lund, Sweden. ⁶Department of Genetics, Hospices Civils de Lyon, Bron, France. ⁷Department of Medical Genetics, Medical School, University of Athens, Athens, Greece. ⁸Biochemistry Laboratory, University hospital of Besançon, Besançon, France. ⁹Department of Medical Oncology and CIC-BT506, University Hospital of Besançon, Besançon, France. ¹⁰Department of Pediatric Hemato-Oncology, University Hospital of Nice, Nice, France.

Received: 25 August 2014 Accepted: 20 October 2014

Published online: 07 November 2014

References

1. Pober BR: Williams-Beuren syndrome. *N Engl J Med* 2010, **362**:239–252.
2. Vanhapiha N, Knuutila S, Vettenranta K, Lohi O: Burkitt lymphoma and Ewing sarcoma in a child with Williams syndrome. *Pediatr Blood Cancer* 2014, **61**:1877–1879.
3. Chonan M, Kanamori M, Kumabe T, Saito R, Watanabe M, Tominaga T: Pilocytic astrocytoma of the cerebellum with Williams syndrome: a case report. *Childs Nerv Syst ChNS Off J Int Soc Pediatr Neurosurg* 2013, **29**:1211–1214.
4. Zhukova N, Naqvi A: Williams-Beuren Syndrome and Burkitt Leukemia. *J Pediatr Hematol Oncol* 2013, **35**:e30–e32.
5. Onimoe GI, Kahwash S, Termuhlen A, Gross TG, Varga E, Rose MJ: Bilateral burkitt lymphoma of the ovaries: a report of a case in a child with williams syndrome. *Case Reports Med* 2011, **2011**:327263.

6. Urisarri-Ruiz Cortázar A, Calvo MG, Donsión MV, Iraola GA, Sánchez JMC: **Renal dysplasia/hypoplasia, Williams Syndrome phenotype and non-Hodgkin lymphoma in the same patient: only a coincidence?** *Pediatr Nephrol Berl Ger* 2009, **24**:1081–1084.
7. Thornburg CD, Roulston D, Castle VP: **Burkitt lymphoma and Williams syndrome: a model for children with a multisystem disorder and malignancy.** *J Pediatr Hematol Off J Am Soc Pediatr Hematol* 2005, **27**:109–111.
8. Amenta S, Moschovi M, Sofocleous C, Kostaridou S, Mavrou A, Fryssira H: **Non-Hodgkin lymphoma in a child with Williams syndrome.** *Cancer Genet Cytogenet* 2004, **154**:86–88.
9. Culic V, Culic S, Armanda V, Resic B, Lasan R, Peterlin B: **Single signal of the Williams syndrome chromosome region 1 gene in hyperpliodic bone marrow cells of acute lymphoblastic leukemia in a Williams syndrome patient.** *Med Pediatr Oncol* 2002, **38**:205–207.
10. Semmekrot BA, Rotteveel JJ, Bakker-Niezen SH, Logt F: **Occurrence of an astrocytoma in a patient with Williams syndrome.** *Pediatr Neurosci* 1985, **12**:188–191.
11. Holmfeldt L, Wei L, Diaz-Flores E, Walsh M, Zhang J, Ding L, Payne-Turner D, Churchman M, Andersson A, Chen S-C, McCastlain K, Becksfort J, Ma J, Wu G, Patel SN, Heatley SL, Phillips LA, Song G, Easton J, Parker M, Chen X, Rusch M, Boggs K, Vadodaria B, Hedlund E, Drenberg C, Baker S, Pei D, Cheng C, Huether R, et al: **The genomic landscape of hypodiploid acute lymphoblastic leukemia.** *Nat Genet* 2013, **45**:242–252.
12. De Vos M, Hayward BE, Picton S, Sheridan E, Bonthron DT: **Novel PMS2 pseudogenes can conceal recessive mutations causing a distinctive childhood cancer syndrome.** *Am J Hum Genet* 2004, **74**:954–964.
13. Xiao A, Li H, Shechter D, Ahn SH, Fabrizio LA, Erdjument-Bromage H, Ishibe-Murakami S, Wang B, Tempst P, Hofmann K, Patel DJ, Elledge SJ, Allis CD: **WSTF regulates the H2A.X DNA damage response via a novel tyrosine kinase activity.** *Nature* 2009, **457**:57–62.
14. Pathania S, Nguyen J, Hill SJ, Scully R, Adelmant GO, Marto JA, Feunteun J, Livingston DM: **BRCA1 is required for postreplication repair after UV-induced DNA damage.** *Mol Cell* 2011, **44**:235–251.
15. Fattah FJ, Hara K, Fattah KR, Yang C, Wu N, Warrington R, Chen DJ, Zhou P, Boothman DA, Yu H: **The transcription factor TFII-I promotes DNA translesion synthesis and genomic stability.** *PLoS Genet* 2014, **10**:e1004419.
16. Savina NV, Smal MP, Kuzhir TD, Egorova TM, Khurs OM, Polityko AD, Goncharova RI: **Chromosomal instability at the 7q11.23 region impacts on DNA-damage response in lymphocytes from Williams-Beuren syndrome patients.** *Mutat Res* 2011, **724**:46–51.
17. Potter N, Karakoula A, Phipps KP, Harkness W, Hayward R, Thompson DNP, Jacques TS, Harding B, Thomas DGT, Palmer RW, Rees J, Darling J, Warr TJ: **Genomic deletions correlate with underexpression of novel candidate genes at six loci in pediatric pilocytic astrocytoma.** *Neoplasia New York N* 2008, **10**:757–772.
18. Conde L, Riby J, Zhang J, Bracci PM, Skibola CF: **Copy number variation analysis on a non-Hodgkin lymphoma case-control study identifies an 11q25 duplication associated with diffuse large B-cell lymphoma.** *PLoS One* 2014, **9**:e105382.
19. Scholtysik R, Kreuz M, Klapper W, Burkhardt B, Feller AC, Hummel M, Loeffler M, Rosolowski M, Schwaenen C, Spang R, Stein H, Thoms C, Trümper L, Vater I, Wessendorf S, Zenz T, Siebert R, Küppers R, Molecular Mechanisms in Malignant Lymphomas Network Project of Deutsche Krebshilfe: **Detection of genomic aberrations in molecularly defined Burkitt's lymphoma by array-based, high resolution, single nucleotide polymorphism analysis.** *Haematologica* 2010, **95**:2047–2055.
20. Chang C-C, Zhou X, Taylor JJ, Huang W-T, Ren X, Monzon F, Feng Y, Rao PH, Lu X-Y, Fabio F, Hilsenbeck S, Creighton CJ, Jaffe ES, Lau C-C: **Genomic profiling of plasmablastic lymphoma using array comparative genomic hybridization (aCGH): revealing significant overlapping genomic lesions with diffuse large B-cell lymphoma.** *J Hematol Oncol J Hematol Oncol* 2009, **2**:47.
21. Sung CO, Choi CH, Ko Y-H, Ju H, Choi Y-L, Kim N, Kang SY, Ha SY, Choi K, Bae D-S, Lee J-W, Kim T-J, Song SY, Kim B-G: **Integrative analysis of copy number alteration and gene expression profiling in ovarian clear cell adenocarcinoma.** *Cancer Genet* 2013, **206**:145–153.
22. Hess J, Thomas G, Braselmann H, Bauer V, Bogdanova T, Wienberg J, Zitzelsberger H, Unger K: **Gain of chromosome band 7q11 in papillary thyroid carcinomas of young patients is associated with exposure to low-dose irradiation.** *Proc Natl Acad Sci U S A* 2011, **108**:9595–9600.
23. Chariyalertsak S, Khuhaprema T, Bhudisawasdi V, Sripa B, Wongkham S, Petmitr S: **Novel DNA amplification on chromosomes 2p25.3 and 7q11.23 in cholangiocarcinoma identified by arbitrarily primed polymerase chain reaction.** *J Cancer Res Clin Oncol* 2005, **131**:821–828.
24. Buhard O, Cattaneo F, Wong YF, Yim SF, Friedman E, Flejou J-F, Duval A, Hamelin R: **Multipopulation analysis of polymorphisms in five mononucleotide repeats used to determine the microsatellite instability status of human tumors.** *J Clin Oncol Off J Am Soc Clin Oncol* 2006, **24**:241–251.

doi:10.1186/s13045-014-0082-4

Cite this article as: Guenat et al.: Constitutional and somatic deletions of the Williams-Beuren syndrome critical region in Non-Hodgkin's Lymphoma. *Journal of Hematology & Oncology* 2014 **7**:82.

Submit your next manuscript to BioMed Central and take full advantage of:

- Convenient online submission
- Thorough peer review
- No space constraints or color figure charges
- Immediate publication on acceptance
- Inclusion in PubMed, CAS, Scopus and Google Scholar
- Research which is freely available for redistribution

Submit your manuscript at
www.biomedcentral.com/submit

