Arachnomelia in Brown Swiss cattle maps to chromosome 5

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Abstract Arachnomelia in Brown Swiss cattle is a
monogenic autosomal recessive inherited congenital dis-
order of the skeletal system giving affected calves a spidery
look (OMIA ID 000059). Over a period of 20 years 15
cases were sampled in the Swiss and Italian Brown cattle
population. Pedigree data revealed that all affected indi-
viduals trace back to a single acknowledged carrier founder
sire. A genome scan using 240 microsatellites spanning the
29 bovine autosomes showed homozygosity at three adja-
cent microsatellite markers on bovine Chr 5 in all cases.
Linkage analysis confirmed the localization of the arach-
nomelia mutation in the region of the marker *ETH10*. Fine-
mapping and haplotype analysis using a total of 34 markers
in this region refined the critical region of the arachnomelia
locus to a 7.19-Mb interval on bovine Chr 5. The disease-
associated IBD haplotype was shared by 36 proven carrier
animals and allows marker-assisted selection. As the

corresponding human and mouse chromosome segments do
not contain any clear functional candidate genes for this
disorder, the mutation causing arachnomelia in the Brown
Swiss cattle might help to identify an unknown gene in
bone development.

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Introduction

Inherited bovine arachnomelia, also termed syndrome of
arachnomelia and arthrogryposis, is a congenital abnor-
mality of the skeletal system giving affected calves a
spidery look (spider-legs; OMIA ID 000059; Fig. 1). The
bones of the legs appear to be more fragile than normal and
spontaneous fracture during calving may injure the dam.
Arachnomelia-affected calves are delivered full term and
born dead or die soon after birth. The most important
pathologic findings are facial deformities, bone dolicho-
stenomelia, angular deformities in the distal part of the
hind legs, muscular atrophy, and sometimes cardiac mal-
formations (Testoni and Gentile 2004). In addition to single
unrelated cases of arachnomelia-affected Holstein cattle,
recessive inherited arachnomelia was initially reported in
German Fleckvieh cattle (Rieck and Schade 1975).
Recently, more than 140 cases of arachnomelia-affected
calves were reported in the Bavarian Simmental population
which all traced back to a single founder (Buitkamp et al.
2008). An outbreak of arachnomelia in the European
Brown cattle population occurred during the 1980 s after
the improvement of the local Brown cattle breeds by
extensive usage of highly selected American Brown Swiss
sires (Brem et al. 1984; König et al. 1987; Lidauer and Essl
1994). There is no relationship between the putative
founder animals that introduced the arachnomelia mutation

Fig. 1 Arachnomelia in a Brown Swiss calf

in Simmental and Brown Swiss cattle, respectively. Arachnomelia (A) in Brown Swiss follows an autosomal monogenic recessive inheritance with full penetrance, and a control breeding program based on the identification of heterozygous carriers by pedigree analyses was established in Switzerland in 1985 (König et al. 1987). However, there are still A-carriers within the international Brown Swiss cattle population. Recently, four cases of arachnomelia were reported from Italy (Testoni and Gentile 2004). Initially, it seemed that the pathogenesis of bovine arachnomelia resembled that of human Marfan syndrome (Rieck and Schade 1975). However, recent clinical findings recorded in arachnomelia-affected calves differ from the typical picture of human Marfan patients (Testoni and Gentile 2004). Moreover, a different phenotype, more closely resembling human Marfan syndrome, has recently been described in cattle harboring a disease-causing mutation in the bovine *FBN1* gene (Singleton et al. 2005).

The aim of this study was to localize the genetic locus responsible for arachnomelia in Brown Swiss cattle. We therefore performed a microsatellite-based genome scan

and subsequently fine-mapped the linked chromosome region by analysis of additional markers from the bovine genome sequence combined with haplotype analysis and the identification of recombinant chromosomes.

Material and methods

Animals

A total of 15 calves (7 females, 8 males) with the clinical and pathologic diagnosis of arachnomelia and their available ancestors were sampled in the Brown Swiss cattle population of Italy and Switzerland between 1988 and 2007. A total of 36 acknowledged A-carriers, classified as obligate heterozygotes, that have recorded arachnomelia offspring and are related to the assumed founder of the established family were collected (Fig. 2). In addition, samples of 13 progeny-tested noncarrier sires related to the founder sire of the family were available. Genomic DNA was obtained from blood, semen, or tissue using the DNeasy Blood & Tissue Kit (Qiagen, Valencia, CA). The initial genome scan was performed using a subset of 8 affected and 19 A-carrier animals (Fig. 2). The subsequent fine-mapping studies were performed on the entire animal set.

Microsatellite genotyping

Two hundred forty microsatellite markers taken from the latest bovine genetic map were used for the genome scan (Ihara et al. 2004; Supplementary Table 1). The order of the markers and map distances were based on the cattle genome sequence (build 4.0). These 240 markers covered all 29 autosomes with an average spacing of 10.6 Mb. Microsatellite markers were amplified using the Multiplex PCR Kit (Qiagen) and fragment size analyses were determined on an ABI 3730 capillary sequencer (Applied
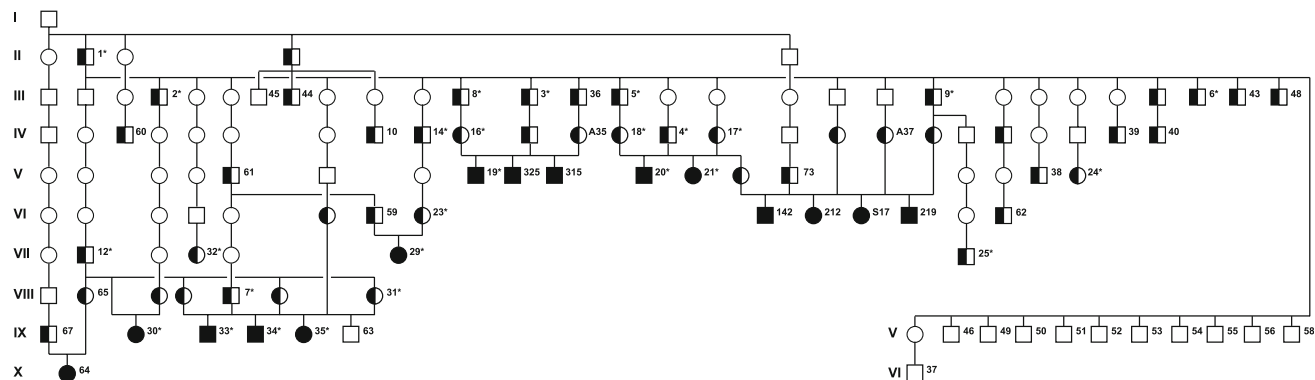
Fig. 2 Ten-generation pedigree of the Brown Swiss cattle family segregating for arachnomelia. Affected animals are filled symbols and obligate heterozygous animals are half-filled. Animals that were included in the genome scan are indicated with a star

Table 1 Association analyses using χ^2 tests for ten microsatellite markers and arachnomelia in Brown Swiss cattle

Marker	Chr	Genomic position (Mb)	Controls		Affecteds		χ^2 tests for association			Error probability		
			n	Alleles	n	alleles	Genotype	Allele	Trend	Genotype	Allele	Trend
BMS711	1	20.12	19	4	8	4	15.952	8.872	6.893	0.026	0.031	0.075
DIK4673	2	62.9	18	6	7	3	12.316	13.948	11.335	0.264	0.016	0.045
RM500	5	51.91	19	3	8	1	2.584	2.320	2.584	0.108	0.128	0.108
BR2936	5	56.35	19	4	8	1	10.556	7.209	10.556	0.014	0.066	0.014
ETH10	5	60.84	19	4	8	1	19.326	10.447	19.326	0.000	0.015	0.000
DIK4606	7	35.12	19	6	7	5	12.870	11.942	9.259	0.379	0.036	0.099
ETH7	13	55.21	19	4	8	1	2.584	3.386	2.584	0.460	0.336	0.460
RM327	13	60.8	19	7	8	5	19.806	15.835	14.994	0.071	0.015	0.020
CSSM66	14	3.94	19	9	8	8	23.803	6.896	7.471	0.033	0.548	0.487
BMS462	16	73.87	19	4	8	1	0.798	0.766	0.798	0.671	0.682	0.671

Biosystems, Foster City, CA) and analyzed with the GeneMapper 4.0 software (Applied Biosystems).

For fine-mapping, new microsatellite markers in the linked region of Chr 5 were developed by Tandyman search (http://snp.lanl.gov/tandyman/cgi-bin/tandyman.cgi) using the bovine genome sequence (Supplementary Table 2). The sequences of the Chr 5 markers were anchored to the human genome sequence (build 36) using BLASTN.

Data analysis

Correctness of Mendelian inheritance of markers was confirmed using Pedstats software (Wigginton and Abecasis 2005). The ALLELE procedure of the software package SAS/Genetics (ver. 9.1.3; SAS Institute Inc., Cary, NC) was used to calculate the number of alleles, the observed heterozygosity, and the polymorphism information content (PIC) of the markers. Preliminary association analyses were performed using the CASECONTROL procedure of SAS/Genetics, which tests for dominant allele effects on the disease penetrance, and the allele case-control test and the linear trend test, which test for additive allele effects on the disease penetrance. Multipoint parametric linkage analysis under the assumption of arachnomelia segregating as a biallelic autosomal recessive trait with complete penetrance was performed with Merlin software ver. 1.1.2 (Abecasis et al. 2002). A frequency of 0.01 was assumed for the mutated allele. The pedigree was split into two subpedigrees due to the high proportion of missing DNA samples. The LOD score test statistic was used to estimate the proportion of linked families (α) and the corresponding maximum heterogeneity LOD score. To reconstruct the most likely haplotypes and identify recombinations, we applied the "best" option of Merlin software and the Haplopainter software for visualization (Thiele and Nürnberg 2005).

Results and discussion

We compiled a pedigree of a Brown Swiss cattle family segregating for arachnomelia (A), which was consistent with monogenic autosomal recessive inheritance (Fig. 2). All 15 affected calves were inbred from a probable founder sire named *Norvic Larry's LILASON*, born in 1957. The founding mutation thus probably occurred four to nine generations before the cases occurred. The arachnomelia mutation was probably introduced by *LILASON*, as until now all acknowledged A-carriers can be traced back to this American Brown Swiss artificial insemination (AI) bull (Fig. 2). In particular, his son *Norvic Lilason's BEAUTI-CIAN*, born in 1960 (animal No. 1; Fig. 2), was earlier recognized as responsible for the worldwide diffusion of the defect in the Brown cattle breed (König et al. 1987). This popular AI sire disseminated the deleterious mutation, and inbreeding among the descendants increased the likelihood of arachnomelia emerging. After recognition of arachnomelia, frequencies of approximately 3% for the mutant A allele were estimated in the AI-derived Brown cattle populations of Switzerland and Austria (Fuschini et al. 1992; Lidauer and Essl 1994). As two proven A-carrier AI sires (*Prealba Pete Rose AMARANTO* and *Superbrown Caod TOMMY-ET*, animals No. 7 and 12; Fig. 2) of the current cases have been widely used in recent decades, further cases of the disease are expected. In light of the pedigree information, we hypothesized that the 15 arachnomelia-affected individuals of the established Brown Swiss cattle family would likely be homozygous for a common chromosome segment flanking the A locus. Therefore, we applied a homozygosity mapping approach to identify the genome region harboring the disease-causing mutation (Charlier et al. 1996, 2008).

We performed a microsatellite-based genome scan using 8 arachnomelia-affected calves and 19 proven carriers. The markers used for the whole-genome scan showed a mean

Table 2 Disease-associated haplotypes (shaded columns) of 34 microsatellites of Chr 5 in 15 homozygous arachnomelia-affected calves and 36 heterozygous A-carriers

Marker	Chr 5 (Mb)	affected animals										A-carriers						
		(4)	(2)	(2)	(1)	(1)	(1)	(1)	(1)	(1)	(1)	(21)	(5)	(4)	(2)	(2)	(1)	(1)
BMC1009	30.53		280	280									280	280		280	280		
SAA17	39.09		261	261									261	261		261	261		
DIK4782	40.85		168	168					168	168			168	168		168	168		
SAA18	44.49		167	167					167	167			167	167		167	167		
SAA19	50.15	268	268	268	268		268	268	268	268	268	268	268	268	268	268	268	
BMS1617	51.89	164	164	164	164	164	164	164	164	164	164	164	164	164	164	164	164	
RM500	51.91	124	124	124	124	124	124	124	124	124	124	124	124	124	124	124	124	
DIK2732	55.83	205	205	205	205	205	205	205	205	205	205	205	205	205	205	205	205	
DIK2410	56.27	186	186	186	186	186	186	186	186	186	186	186	186	186	186	186	186	
BR2936	56.35	154	154	154	154	154	154	154	154	154	154	154	154	154	154	154	154	
SAA20	56.74	112	112	112	112	112	112	112	112	112	112	112	112	112	112	112	112	
BMS490	57.29	181	181	181	181	181	181	181	181	181	181	181	181	181	181	181	181	
SAA21	58.14	205	205	205	205	205	205	205	205	205	205	205	205	205	205	205	205	205
SAA01	58.21	180	180	180	180	180	180	180	180	180	180	180	180	180	180	180	180	180
SAA07	58.48	163	163	163	163	163	163	163	163	163	163	163	163	163	163	163	163	163
SAA02	59.71	188	188	188	188	188	188	188	188	188	188	188	188	188	188	188	188	188
SAA03	60.53	236	236	236	236	236	236	236	236	236	236	236	236	236	236	236	236	236
ETH10	60.84	216	216	216	216	216	216	216	216	216	216	216	216	216	216	216	216	216
SAA04	61.46	230	230	230	230	230	230	230	230	230	230	230	230	230	230	230	230	230
SAA05	61.87	149	149	149	149	149	149	149	149	149	149	149	149	149	149	149	149	149
AGLA254	63.99	194	194	194	194	194	194	194	194	194	194	194	194	194	194	194	194	194
SAA11	64.09	189	189	189	189	189	189	189	189	189	189	189	189	189	189	189	189	189
SAA13	64.48	226	226		226	226	226	226	226			226	226	226	226	226	226	226
DIK5248	66.08	199	199		199	199	199	199				199	199	199	199	199	199	199
CSSM022	66.55	219	219		219	219	219	219				219	219	219	219	219	219	219
SAA16	67.40	221	221		221	221	221	221				221	221	221	221	221	221	221
BMS1216	76.37	141	141		141	141	141	141				141	141	141	141	141	141	141
DIK5165	76.76	238	238		238	238	238	238				238	238	238	238		238	238
RM029	80.42	82	82		82	82	82	82				82	82	82	82		82	82
DIK545	88.27	127	127		127	127	127					127	127	127			127	127
DIK1048	90.42	122	122		122	122	122					122	122	122			122	122
BMS1248		134	134		134	134						134	134	134				134
DIK4329	96.03	201	201		201	201						201	201	201				201
BM315	104.05	112										112						112

Numbers in parentheses are the number of animals showing the specific haplotype. A block of ten perfectly associated markers representing the 7.19-Mb interval containing the A locus is framed

number of 5.3 alleles and an average polymorphism information content (PIC) of 0.57 (Supplementary Table 1). Therefore, they were supposed to be appropriate for disease gene mapping in our inbred family. Of 240 autosomal microsatellite markers tested, five were homozygous in all affected animals (Table 1). Three of these five markers, *RM500*, *BR2936*, and *ETH10*, were colocalized on the central part of bovine Chr 5, and one of them (*ETH10*) was significantly associated ($p < 0.01$) with the arachnomelia phenotype (Table 1). The reduction of heterozygosity within the affected calves was complemented by the finding that the 19 genotyped carriers showed at least one copy of the allele, which was present in all eight

cases at the three neighboring bovine Chr 5 markers *RM500*, *BR2936*, and *ETH10*. Five additional markers were also associated with arachnomelia with $p < 0.05$ (Table 1). However, as these five markers showed three to eight different alleles in the eight closely related cases and mapped to five different cattle chromosomes, they did not fit the hypothesis of a single chromosomal region of identity-by-descent (IBD) in all affected calves. To verify the results of the preliminary association study, we performed a linkage analysis that confirmed the localization of the A locus on bovine Chr 5. Markers with linkage in both subfamilies were observed only on Chr 5. The highest LOD score of 1.11 was observed at marker *ETH10*. No
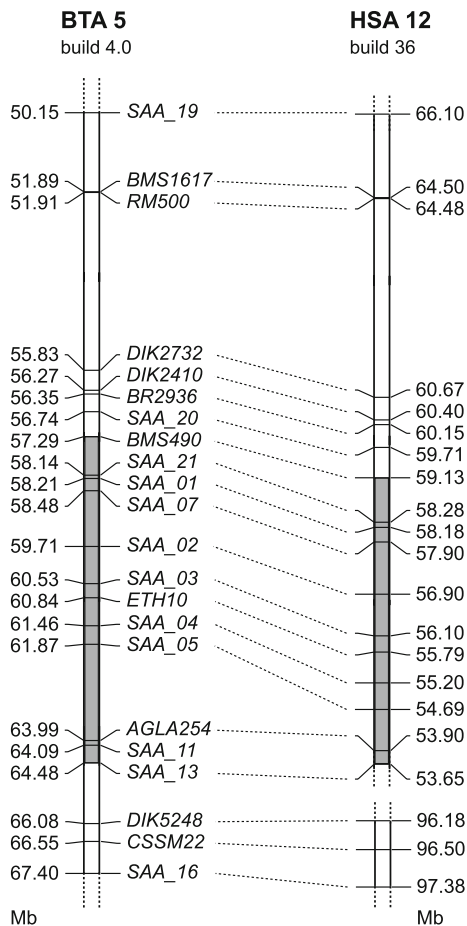
Fig. 3 Comparative map of bovine Chr 5 and human Chr 12. The Mb positions of selected microsatellites of this study are indicated with respect to the bovine genome assembly (build 4.0). All markers were anchored by BLASTN searches on the human genome (build 36.3). The 7.19-Mb interval harboring the arachnomelia mutation is shaded

indication of significant linkage was detected on the other chromosomes (Supplementary Fig. 1).

Subsequently, we fine-mapped this region by examination of additional markers in extended-family material including 15 affected calves, 36 proven A-carriers, and 13 proven noncarriers (Fig. 2). We took 20 markers from the linkage map of bovine Chr 5 and developed 14 new microsatellite markers from the bovine genome sequence. Parametric linkage analysis using the extended pedigree and additional markers confirmed the initial genome-wide results with a maximal LOD score of 9.21 ($\alpha = 1$) at marker *SAA21*. We then calculated the most likely haplotypes at 34 Chr 5 microsatellites for all 64 available family members. All 15 affected calves were homozygous at 17 markers from *BMS1617* to *SAA11*, which allowed the identification of a single disease-associated haplotype, narrowing the critical region to 14.3 Mb between *SAA19* and *SAA13* (Table 2). Subsequently, we reconstructed the arachnomelia-associated haplotype for each obligate

heterozygous animal. The previously established IBD haplotype was shared by 35 assumed A-carriers (Table 2), and 13 proven noncarriers received the entire wild-type haplotype from their A-carrying father or mother. One son of *BEAUTICIAN* (animal No. 6; Fig. 2), who sired at least two recorded arachnomelia-affected offspring, inherited a recombinant haplotype from his father. Thus, based on this single recombinant chromosome, the most likely position of the A locus on Chr 5 is between *BMS490* as the centromeric boundary and *SAA13* as the telomeric boundary (Table 2). These markers flank a 7.19-Mb segment between positions 57.29 and 64.48 Mb on Chr 5 (build 4.0).

BLAST searches of the bovine markers with respect to the human genome (Supplementary Table 2) established a sequence-based framework for comparing the bovine and human genomes (Fig. 3). The bovine A-locus-containing interval corresponds to a syntenic 5.48-Mb interval on human Chr 12 between 53.65 and 59.13 Mb. This human segment contains 127 genes, including a cluster of 29 olfactory receptor genes and 20 annotated hypothetical loci (build 36.3). These genes and also the information of the corresponding genes on the syntenic mouse Chr 10 segment were screened for any known involvement in bone development. The human growth differentiation factor 11 gene (*GDF11*) resides at 54.42 Mb on human Chr 12 and is a member of the bone morphogenetic protein family and the TGF-β superfamily, which are regulators of cell growth and differentiation in both embryonic and adult tissues. *Gdf11*-deficient embryos show anterior-posterior patterning defects and suggest that this protein is involved in mesodermal formation during embryonic development (McPherron et al. 1999). The resequencing of bovine *GDF11* at 62.07 Mb on bovine Chr 5 using DNA of affected and healthy Brown Swiss cattle revealed no sequence polymorphism within the three coding exons and flanking intron regions (data not shown). Further investigations into other genes in the region of interest did not suggest any other clear candidate genes. Therefore, either a noncoding mutation of the *GDF11* gene or a mutation in an as yet unknown bone development gene is probably responsible for arachnomelia in cattle.

In recent decades, outbreaks of four undesirable genetic defects (weaver disease, spinal dysmyelination, spinal muscular atrophy, arachnomelia) have occurred in Brown Swiss cattle (http://omia.angis.org.au). The arachnomelia disease is the only defect for which neither an indirect nor a direct DNA test to detect the carriers is available (Georges et al. 1993; Krebs et al. 2007; Nissen et al. 2001). Therefore, the established phase of Chr 5 marker alleles provides a set of flanking and closely linked markers for marker-assisted selection. In many cases, an indirect DNA test is reasonably accurate and gives a reliable indication of the disease

genotype of an animal. In our case, the markers are linked to the disease-causing mutation, although in some cases, discussed below, they are not sufficiently specific for a diagnostic test. The linked marker alleles have a reduced association with the causative mutation as they occur also on nonmutant chromosomes. Both within the presented family and during our on-going genetic testings we identified some A-carriers that shared two copies of the disease-associated haplotype. The marker genotypes of these animals look completely homozygous, exactly as in arachnomelia-affected calves. For example, the bull *TOMMY* (animal No. 12; Fig. 2) is homozygous at 28 markers from *SAA19* to *BMS1248*, covering about 40 Mb of Chr 5, and the bull *DIQU* (animal No. 73; Fig. 2) is homozygous at 19 markers from *SAA18* to *SAA11*, covering about 30 Mb of Chr 5. A possible explanation is apparent from the pedigree of these animals, because both bulls are inbred to the father of the founder sire of our family presented in Fig. 2 (Supplementary Fig. 2). They probably got the disease-associated haplotype from the assumed arachnomelia founder *LILA-SON* and the second haplotype without the A mutation was transmitted independently through several generations from the father of the founder (Supplementary Fig. 2). Experimental evidence for this segregation pattern was provided by genotyping the respective markers in three available male ancestors of *TOMMY*. These progeny-tested and widely used AI bulls were not registered as carriers of the arachnomelia mutation, but reconstruction of their haplotypes revealed the presence of the A-associated haplotype seen in affected calves. We think that these observations might explain the homozygosity of arachnomelia-linked Chr 5 markers in unaffected cattle. According to this hypothesis, the mutation occurred on a common haplotype that was spread into the Brown Swiss breed by *Lee's Hill MAS-TERPIECE*, the father of *LILASON*. This name can be found in numerous pedigrees of highly frequented AI bulls. These findings make it possible to exactly date the causal mutation event, which must have occurred during the spermiogenesis of *MASTERPIECE* or during the early embryonic development of *LILASON*. The relatively young age of the mutation is also consistent with the extended homozygosity in the examined arachnomelia-affected calves as only a small number of recombination events have shortened the ancestral wild-type haplotype during four to nine meioses.

Genome-wide association analysis using whole-genome single nucleotide polymorphism (SNP) arrays is now emerging as a powerful method for high-resolution mapping of loci controlling phenotypic traits in domestic animals (Andersson 2008). In a recent proof-of-principle study, Charlier et al. (2008) have used this approach to identify the mutations underlying three monogenic recessive inherited diseases in cattle. A targeted genotyping of Chr 5 SNPs might help to slightly reduce the critical interval of the arachnomelia mutation by fine-mapping recombination events. Furthermore, SNPs may be used for improvement of indirect DNA testing once heterozygous markers are detected in carriers that are homozygous for the microsatellites. Progression from an indirect DNA test to a direct DNA test will require further research. It is difficult to predict the effort required to make this progression because of the high number of positional candidate genes within the identified 7.19-Mb region. The identification of the causative gene may reveal new insights into fundamental processes of bone differentiation. Therefore, the bovine arachnomelia phenotype represents an excellent naturally occurring model showing a complex developmental defect that can possibly be explored for a better understanding of similar defects in humans.

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