

Molecular Analysis of Desmoid Tumors with a High-Density Single-Nucleotide Polymorphism Array Identifies New Molecular Candidate Lesions

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Keywords

Desmoid tumors · Genomic profiling · APC · CUB and Sushi multiple domains 1 (CSMD1)

Summary

Background: Desmoid tumors are neoplastic proliferations of connective tissues. The mutation status of the gene coding for catenin (cadherin-associated protein) beta 1 (CTNNB1) and trisomy 8 on the chromosomal level have been described to have prognostic relevance. **Patients and Methods:** In order to elucidate new molecular mechanisms underlying these tumors, we carried out a molecular analysis with a genome-wide human high-density single-nucleotide polymorphism (SNP) array, in 9 patients. **Results:** Single samples showed numerical aberrations on chromosomes (Chrs) 20 and 6 with either trisomy 20 or monosomy 6. No trisomy 8 could be detected. Recurrent heterozygous deletions were found in Chr 5q (including the *APC* gene locus, $n = 3$) and Chr 8p23 ($n = 4$, containing coding regions for the potential tumor suppressor gene *CSMD1*). This novel deletion in 8p23 showed an association with local recurrence. In addition, structural chromosomal changes (gain of Chrs 8 and 20) were found in a minority of cases. **Conclusion:** The genomic alteration affecting the candidate gene *CSMD1* could be important in the development of desmoid tumors.

Introduction

Desmoid tumors are defined as ‘clonal fibroblastic proliferations that arise in the deep soft tissues and are characterized by infiltrative growth and a tendency toward local recurrence

*These two authors contributed equally to this work.

Schlüsselwörter

Desmoide · Genomische Profiling-Analyse · APC · CUB und Sushi multiple Domänen 1 (CSMD1)

Zusammenfassung

Hintergrund: Desmoide sind neoplastische Proliferationen des Bindegewebes. Für diese Tumoren wurde sowohl für den Mutationsstatus des Gens für Catenin (Cadherin-assoziiertes Protein) Beta 1 (CTNNB1) als auch für die Trisomie 8 ein prognostischer Wert beschrieben. **Patienten und Methoden:** Zur Evaluation neuer molekularer Mechanismen in Desmoiden haben wir für 9 Patienten humangenomische Profiling-Analysen auf der Basis eines hochauflösenden Einzelnukleotidpolymorphismen (SNP)-Arrays durchgeführt. **Ergebnisse:** Bei einzelnen Patienten fanden sich in den Chromosomen (Chr) 20 und 6 numerische Aberrationen mit Trisomie 20 oder Monosomie 6, aber es fand sich keine Trisomie 8. Mehrfach wurden heterozygote Deletionen in Chr 5 gefunden (inklusive des *APC*-Lokus, $n = 3$) sowie auf Chr 8p23 (enthält kodierende Abschnitte des potenziellen Tumorsuppressorgens *CSMD1*, $n = 4$). Diese neue Alteration zeigte einen Zusammenhang mit Lokalrezidiven. Zusätzliche strukturelle Aberrationen (Chr 8 und 20) wurden in einzelnen Fällen gefunden. **Schlussfolgerung:** Alterationen wie im Kandidatengen *CSMD1* könnten eine wichtige Rolle in der Entwicklung von Desmoiden spielen.

but an inability to metastasize’ (World Health Organization). They may affect all sites including extremities, trunk, and abdomen [1]. Two different types of desmoid tumors are described: Besides sporadic tumors there is a relationship between desmoids and familial adenomatous polyposis (FAP; Gardner syndrome) [2–4]. Here, a germ-line mutation of *APC* (coding for the adenomatous polyposis coli (APC) protein) predisposes patients to develop multiple colonic polyps and

Table 1. Patient characteristics, clinical information of relapse, genomic alteration profiles of the SNP array findings, and CTNNB1 mutational status in desmoid tumors (n = 9)

Patient number	Gender / Age, years / FAP	Primary localization	Therapy	PFS, months	Relapse	Macroscopic SNP findings > 1 Mbp (n)	Macroscopic findings on chromosome	Microscopic SNP findings < 1 Mbp (n)	Total number of findings	Del 8p (CSMD1)	Del 5q (APC)	CTNNB1 mutation
1 ^a	F / 25 / yes	abdomen	S, R, Ch, Im	17	yes	yes (4)	5, 6, 10, 13	yes (3)	7	yes	yes	WT
2	M / 27 / no	abdomen	S	5	no	no	–	yes (6)	6	yes	no	pT41A
3	F / 39 / no	abdomen	S	12	no	yes (1)	20	yes (3)	4	no	no	pS45P
4	F / 34 / no	abdomen	S	26	no	no	–	yes (7)	7	no	no	pT41A
5	F / 30 / no	abdomen	S, R	24	no	no	–	yes (2)	2	no	no	WT
6 ^a	F / 15 / no	abdomen	S, R, Im	16	yes	no	–	yes (3)	3	yes	no	pT41A
7	F / 39 / no	extremity	S, R	12	no	no	–	yes (1)	1	no	no	pT41A
8 ^a	M / 18 / n.a.	abdomen	S, R	12	yes	yes (2)	5, 5	yes (4)	6	yes	yes	WT
9	F / 73 / no	abdomen	S, R	5	no	yes (1)	5	yes (1)	2	yes	yes	U

FAP = Familial adenomatous polyposis, F = female, M = male, n.a. = not applied, S = surgery, R = radiotherapy, Ch = chemotherapy, A = antihormone therapy, Im = imatinib, PFS = progression-free survival, Mbp = mega base pairs, CSMD1 = CUB and Sushi multiple domains 1, APC = adenomatous polyposis coli, CTNNB1 = catenin (cadherin-associated protein) beta 1, Del = deletion, U = unknown, WT = wild type.
^aPatient with relapse.

extraintestinal neoplasms such as desmoids. Besides the involvement of APC in patients with FAP – where the germline APC mutation is followed by inactivation of the wild-type APC allele – an association of the APC/beta-catenin pathway has been reported for sporadic desmoid tumors [5].

Moreover, the mutation status of the gene coding for catenin (cadherin-associated protein) beta 1 (CTNNB1) has an impact on the prognosis of patients with desmoid tumors. Recent studies indicate that at least 85% of sporadic desmoids showed mutations in this gene. Retrospectively, it was found that one of them, the S45F mutation, was the most important predictor of recurrence after surgery of the primary tumor, with a relative risk of 3.5 [6]. This represents the first documentation of a potentially clinically applicable molecular determinant of desmoids [7].

On the chromosomal level, recurrent cytogenetic alterations include trisomy 8, trisomy 20, and loss of chromosome (Chr) 5q. These cytogenetic alterations are described in 3–30% of all desmoids. Most of the analyses conducted thus far were performed by conventional cytogenetics or comparative genomic hybridization (CGH) arrays. Some authors describe a prognostic impact of alterations such as trisomy 8 or Del 5q [8].

In the present pilot study, we carried out a comprehensive molecular analysis with a high-density single-nucleotide polymorphism (SNP) array in order to elucidate new molecular mechanisms underlying these rare tumors, addressing the following question: Which submicroscopic deletions could be found in desmoid tumors?

Materials and Methods

Patients and Samples

The study included 9 patients with desmoid tumors. The patient characteristics (gender, age, tumor site, treatments) are summarized in table 1. All patients were referred to our outpatient service with the diagnosis of a desmoid tumor confirmed by histology obtained from surgical specimens. Tumor specimens were classified according to the Fédération nationale des centres de lutte contre le cancer (FNCLCC) system [9]. Informed consent was obtained from all patients according to the Declaration of Helsinki. Nucleic acids were isolated from frozen surgical specimens collected at operation, after homogenization of the frozen samples using Cryoprep (Covaris, Woburn, MA, USA).

SNP Array Analysis and Validation

Genomic DNA for SNP array analyses was isolated from diagnostic tumor specimens with the ALLprep DNA/RNA kit (Qiagen, Hilden, Germany) and quality controlled by Nanodrop ND-1000 photometric measurement and evaluation by conventional agarose gel electrophoresis. 500 ng of genomic DNA per sample was processed and hybridized according to the Genome Wide Human SNP 6.0 Array protocol instructions (Affymetrix, Santa Clara, CA, USA). Raw intensity data was processed using the Genotyping Console 4.0 software (Affymetrix). Genotyping files were imported into the CNAG 3.3 software to perform allele-specific copy number analysis as previously described [10–12], using 270 anonymous reference samples generated by the international Hap-Map project. Known copy number polymorphisms were excluded from the data by comparison with known copy number polymorphisms registered in the University of California Santa Cruz (UCSC) genome browser

<http://genome.ucsc.edu/>. Putatively somatically acquired genomic alterations were validated on exemplary lesions by performing allele-specific copy number analysis in matched-pair SNP 6.0 array analysis of DNA from corresponding healthy tissue samples in 5 patients.

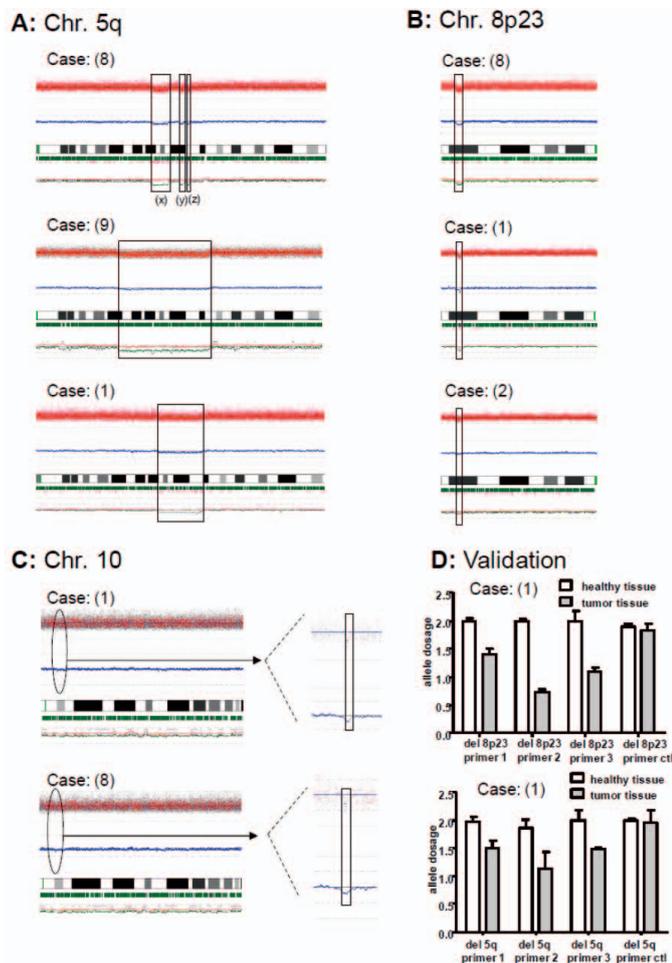


Fig. 1. Representative examples of detected genomic lesions. (A) SNP array profiles of Chr 5 (left) displaying recurrent patterns of deletions in Chr 5 involving the *APC* gene. In the illustration, red dots (top panel) represent single SNP signals; the blue line indicates a smoothed average copy number. Amplifications and deletions are characterized by an upward or downward deviation of the red dots and the blue line, respectively. In case 8, additional small deletions, (y) and (z), could be found. These deletions contain tumor necrosis factor, alpha-induced protein 8 (*TNFAIP8*), and sortin nexin 2 (*SNX2*). (B) SNP array profile of a recurrent submicroscopic deletion that occurred in cases 1, 2 and 8, affecting the region 8p23.2 with parts of the *CSMD1* gene. (C) SNP array profile of a submicroscopic deletion that occurred in cases 1 and 5, affecting the region 10q11 with the annexin 8 gene. (D) Example of a validation set of the 5q and 8p23 deletions by quantitative real-time PCR (qRT-PCR) on genomic DNA. The deletions were validated by performing qRT-PCR on tumor samples with the deletions and compared to corresponding healthy tissue from the same patients. 3 primer pairs were located in the region of deletion (primers 1–3). White bars represent healthy tissue samples and were normalized to a copy number value of 2. Grey bars represent tumor samples and show a reduced copy number. With the control primer pair (Chr 8, Chr 5 ctl region), which amplified regions on Chrs 5 and 8 adjacent to the corresponding deletion, both sample types showed similar copy number values.

Mutational Analysis and Gene Expression Analyses

The *CTNNB1* exon 3 was amplified from genomic DNA (100 ng) using the following primers: BCATF 5'-GGTCTCTGTGAAGACTTGCTC-3' and BCATR 5'-CATGTTCCATCATGGGGTCC-3'. Amplification reactions were undertaken for 35 cycles with an annealing temperature of 55 °C. The sequencing reaction was performed using the amplification primers.

In addition, mutation analyses of suspected lesions were carried out for CUB and Sushi multiple domains 1 (*CSMD1*) and *APC* by direct Sanger sequencing of genomic DNA as described for *APC* [13]. For *CSMD1*, primers were designed to amplify 500-bp-long fragments with a minimum of 30–40 bp of intronic flanking sequence or multiple overlapping sequences in the case of larger exons (primer available on request). Amplification reactions were undertaken for 32 cycles with an annealing temperature of 60 °C. Polymerase chain reaction (PCR) products were analyzed by bidirectional direct sequencing using the amplification primers. Sequencing data were collected on an ABI3130 sequencer (Applied Biosystems, Foster City, CA, USA).

Genomic copy number alterations (CNAs) of Chr 8q (*CSMD1*) and Chr 5q containing the *APC* gene were further validated by performing SYBR green quantitative real-time PCR analysis on genomic DNA of matched healthy samples, using a Roche 480 LightCycler (Roche, Mannheim, Germany). All measurements were conducted in triplicate. Cycling program: 15 min 95 °C, 15 s 94 °C, 30 s 55 °C, 30 s 70 °C, 45 cycles.

Results

Summary of Copy Number and Recurrent Chromosomal Aberrations

The high-density SNP array analysis of 9 desmoid samples yielded a total of 38 putatively somatically acquired genomic CNAs consisting of 15 heterozygous deletions, 23 duplications or amplifications, and no copy number neutral loss of heterozygosity (CNLOH). Overall, 100% of the patients in this cohort showed a CNA, with a median of 4 (range: 1–7; table 2, online supplemental material).

Numerical aberrations were found on Chrs 20 and 6 with either trisomy 20 ($n = 1$) or monosomy 6 ($n = 1$). In another patient, loss of 6q could be observed. Heterozygous deletions were detected on Chr 5q ($n = 3$), Chr 10p ($n = 1$) and Chr 13q ($n = 1$). These macroscopic aberrations larger than 1 Mbp (mega base pairs) could be found in 40% (4/9) of the samples (table 1).

The most common recurrent macroscopic CNAs were detected as heterozygous deletions on Chr 5q (33%; $n = 3/9$) containing the *APC* locus (deletions ranged from 6.1 to 43 Mbp). From the 3 patients with this deletion, 2 showed a local recurrence after 12 and 17 months, respectively. 1 recurrence after surgery could be observed in the remaining patients (table 1).

Furthermore, a recurrent submicroscopic deletion on Chr 8p (44%; $n = 4/9$) between 0.26 and 0.56 Mbp was observed sharing an identical submicroscopic deletion of Chr 8p23.2 containing coding regions of *CSMD1* (minimal deleted region 191 kb; fig. 1). In 3 of 4 patients with this deletion of Chr 8p23.2, a relapse was observed after 12, 16, and 17 months, respectively (table 1). Another recurrent microdeletion affected small regions on Chr 10q11 containing regions of the annexin A8 variant (*ANXA8*, $n = 2$).

Additional submicroscopic duplications were discovered in single samples on Chrs 5q, 7p, and 8p. These contained the coding regions for human epidermal growth factor receptors 1 and 2 (EGFR and HER2) and *RUNX1T1*, the gene coding for runt-related transcription factor 1.

Validation of SNP Array Data, Mutational Analysis

Apart from changes encompassing broad genomic regions, numerous recurrent genomic microlesions smaller than 1 Mbp could be identified (table 1). The most common recurrent microdeletion on Chr 8p23.2 (*CSMD1*) and the deletion of Chr 5q (*APC* locus) were validated in 3 patients with corresponding healthy tissue available by performing quantitative real-time PCR on the genomic DNA to confirm the allelic loss of this region. In addition, mutation analysis of exons 4–6 of the *CSMD1* gene and of the *APC* gene was performed and revealed no new sequence variants (fig. 1). *CTNNB1* mutations were detected in 55% (5/9) of patients as affecting codon 41 (n = 4) and codon 45 (n = 1; table 1).

Discussion

Little is known about chromosomal changes in desmoid tumors. In previous studies, which performed CGH analysis and classical karyotyping, most of the desmoids were described with a normal karyotype in 50–77% of the analyzed samples [8, 14]. Using high-density SNP array analysis, our observation showed copy number changes in every single tumor. However, in 40% of our patients, aberrations larger than 1 Mbp could be observed. Taking into account the different resolution of detection techniques such as conventional cytogenetics and CGH arrays, the results are comparable with previous studies showing that structural and numerical aberrations appeared in a subset of desmoid patients.

In a previous study, CGH loss of Chr 6 or 6q, Chr 5q, gain of Chr 20, and alteration of Chr 8q were observed with a frequency of 3–11% [8] and confirmed previous observations [15, 16]. However, in the literature, the frequency of these aberrations is variable for the loss in Chrs 6 (10–20%) and 5q (5–11%) and the gain in Chrs 8 (3–30%) and 20 (7–30%). In addition, a prognostic impact of trisomy 8 was suggested in 1 of these analyses. In our study, no trisomy 8 was detected. However, the small sample size and patient selection in this rare entity could explain discrepancies. In addition, the different analyses hampering comparison and the influence of culture conditions in cytogenetic studies could be proposed as other reasons. Gain of Chr 8 and Chr 20 might be overestimated because minor abnormal cell clones with trisomy 8 or 20 could have been selected for during tissue culture [8, 14]. The losses of Chr 6 and Chr 5q were comparable in the CGH and our SNP array study. However, few recurrent lesions could be observed.

In a high proportion (30%) of patients, a deletion in Chr 5q was seen. This lesion contains the *APC* gene. Two patients with 5q deletion exhibited a local recurrence after 12 and 17 months, respectively. Only 1 patient without this deletion relapsed during follow-up in our cohort. However, due to the small sample size, this is observational. In a proportion of patients, desmoids are associated with FAP, and germ-line mutations in the *APC* gene are described [17, 18]. In our cohort, 1 patient suffered from FAP. In desmoids, *APC* mutations are found between codons 1445 and 1578 [19]. Therefore, mutation analyses of the *APC* gene were performed but revealed no unknown sequence variant. Besides the involvement of *APC* in patients with FAP – where the germ-line *APC* mutation is followed by inactivation of the wild-type *APC* allele – an association of the *APC*/beta-catenin pathway has been reported for sporadic desmoid tumors [5].

In the literature, the frequency of *CTNNB1* mutation is reported as between 50–85%, and a prognostic impact is described [6, 20]. In our series, the mutation frequency is 55%. Due to the small patient cohort, no prognostic data could be reported in our series. However, none of the patients in our series was found to simultaneously have a *CTNNB1* mutation and a recurrent deletion in Chr 5q. This finding is in line with a previous analysis that alterations in *APC* (Del 5q) and *CTNNB1* mutations do not occur simultaneously [8].

As pointed out, the development of desmoids could be linked to *APC* mutations and loss of 5q, which includes the *APC* locus. Therefore, our findings support previous reports of the involvement of alterations of *APC* and the Wnt pathway, namely *CTNNB1* mutations, in desmoid tumorigenesis. Apart from these known aberrations, novel submicroscopic changes were detected in our present pilot series.

The most frequent one of these alterations was a small heterozygous deletion on Chr 8p23.2 (n = 4) containing the coding region of *CSMD1*. This gene spans over 2 Mb of genomic DNA and contains 71 exons. The gene codes for a 3565-amino acid protein consisting of 14 CUB and 28 Sushi domains. *CSMD1* was predicted as a receptor for unknown ligands involved in signal transduction [21]. Its gene is highly expressed in the central nervous system of rats and, in addition, it is also expressed at lower levels in areas of regenerative growth including epithelial cells of the gastrointestinal system, skin, and mammary ducts [10]. Loss of this potential tumor suppressor gene has been observed in several cancers such as prostate [22], head and neck, breast [11, 23, 24], and colon cancer. Interestingly, this lesion has not been described previously in desmoid tumors. The minimal deleted region in involved patients includes 0.26 Mbp containing exons 4–6. Besides the deletion of this gene, point mutations and epigenetic modification leading to loss of *CSMD1* transcripts have been described [11, 12, 24]. Therefore, mutational analysis was performed, but no unknown sequence variant could be detected. In addition, a prognostic impact of this loss on 8p23

is described in head and neck cancer and breast carcinoma [25, 26]. Our results showed an association of this loss with local recurrence. Because of the small patient cohort, variable tumor localizations, and variable therapies, further validation is needed to investigate the role of this inactivation and its prognostic value in this rare entity.

Conclusions

We describe a comprehensive genomic profiling of DNA from patients with desmoids. In addition to the confirmed frequency of known aberrations such as Chr 5q deletions and *CTNGB1* mutations, structural chromosomal changes (gain of Chrs 8 and 20) were found in a minority of cases. A novel recurrent deletion containing the tumor suppressor gene *CSMD1*, which was frequent in relapsing patients, was detected in our pilot series. Therefore, our data may help to pro-

vide better insights into the molecular mechanisms underlying the development of desmoid tumors.

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Disclosure Statement

We declare that we have no conflict of interest.

Online Supplementary Table

Table 2. Summary of duplications, amplifications, and deletions found in desmoid tumor patients (n = 9) by SNP array analysis.

To access the table, please refer to: www.karger.com/DOI=343744.

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