Somatic MED12 mutations in uterine leiomyosarcoma and colorectal cancer

K Kämpäärvi1,9, N Mäkinen1,9, O Kilpivaara1, J Arola2, H-R Heinonen1, J Böhm1, O Abdel-Wahab4, HJ Lehtonen1, LM Pelttari3, M Mehine1, H Schreve4, H Nevanlinna4, RL Levine4, P Hokland7, T Böhling2, J-P Mecklin8, R Büttzow2, LA Aaltonen1 and P Vahteristo*,1

1Department of Medical Genetics, Genome-Scale Biology Research Program, University of Helsinki, PO Box 63, Helsinki FIN-00014, Finland; 2Department of Pathology, The Laboratory of Helsinki University Central Hospital (HUSLAB), Helsinki University Central Hospital and Haartman Institute, University of Helsinki, PO Box 21, Helsinki FIN-00014, Finland; 3Department of Pathology, Jyväskylä Central Hospital, Keskusaari, Jyväskylä FIN-40620, Finland; 4Human Oncology and Pathogenesis Program, Memorial Sloan-Kettering Cancer Center, 1275 York Avenue, Box 20, New-York, NY 10065, USA; 5Department of Obstetrics and Gynecology, University of Helsinki and Helsinki University Central Hospital, PO Box 700, Helsinki, Finland FIN-00029, Finland; 6Department of Developmental Genetics, Max Planck Institute for Molecular Genetics, Ihnestrasse 73, Berlin 14195, Germany; 7Department of Hematology, Aarhus University Hospital, Tage-Hansens Gade 2, Aarhus C DK-8000, Denmark; 8Department of Surgery, Jyväskylä Central Hospital and University of Eastern Finland, Keskusaari, Jyväskylä FIN-40620, Finland

BACKGROUND: Mediator complex participates in transcriptional regulation by connecting regulatory DNA sequences to the RNA polymerase II initiation complex. Recently, we discovered through exome sequencing that as many as 70% of uterine leiomyomas harbour specific mutations in exon 2 of mediator complex subunit 12 (MED12). In this work, we examined the role of MED12 exon 2 mutations in other tumour types.

METHODS: The frequency of MED12 exon 2 mutations was analysed in altogether 1158 tumours by direct sequencing. The tumour spectrum included mesenchymal tumours (extraterine leiomyomas, endometrial polyps, lipomas, uterine leiomyosarcomas, other sarcomas, gastrointestinal stromal tumours), hormone-dependent tumours (breast and ovarian cancers), haematological malignancies (acute myeloid leukaemias, acute lymphoid leukaemias, myeloproliferative neoplasms), and tumours associated with abnormal Wnt-signalling (colorectal cancers (CRC)).

RESULTS: Five somatic alterations were observed: three in uterine leiomyosarcomas (3/41, 7%; Gly44Ser, Ala38_Leu39ins7, Glu35_Leu36delinsVal), and two in CRC (2/392, 0.5%; Gly44Cys, Ala67Val).

CONCLUSION: Somatic MED12 exon 2 mutations were observed in uterine leiomyosarcomas, suggesting that a subgroup of these malignant tumours may develop from a leiomyoma precursor. Mutations in CRC samples indicate that MED12 may, albeit rarely, contribute to CRC tumorigenesis.

Keywords: MED12; mutation screening; somatic mutation; benign tumours; malignant tumours

Mediator is a large multiprotein complex, which is involved in global as well as gene-specific transcriptional regulation of most protein coding genes. The complex can both activate and repress transcription by connecting transcription factors to the RNA polymerase II initiation complex (Taatjes, 2010). Mediator complex subunit 12 (MED12) gene on Xq13.1 encodes MED12 protein, which together with MED13, CDK8, and Cyclin C comprises a CDK8 submodule of the Mediator. This submodule participates in transcriptional regulation, as well as in scaffold formation and transcription elongation (Galbraith et al, 2010). Mediator complex subunit 12 is an essential regulator of the kinase activity of CDK8 submodule, and the protein directly interacts with various transcription factors (Knuesel et al, 2009; Taatjes, 2010). Mediator complex subunit 12 participates in various molecular pathways, for example, p53 and Wnt/β-catenin pathways, which have central roles in tumour development (Kim et al, 2006; Galbraith et al, 2010).

Uterine leiomyomas, also known as fibroids, are benign smooth muscle tumours that occur in approximately 70% of women by the age of 50 years (Day Baird et al, 2003). Despite their benign nature, these tumours cause various symptoms including abdominal pain, abnormal menstrual bleeding, pregnancy complications, and even infertility. Oestrogen and progesterone dependency is a characteristic feature for uterine leiomyomas, which usually occur in women of reproductive age and typically regress after menopause (Parker, 2007). Several recurrent, albeit infrequent, genetic aberrations have been observed in these tumours, including deletions in chromosome 7q, trisomy of chromosome 12, various rearrangements affecting the high mobility group AT-hook 2 (HMGA2) gene, and structural changes at 6p21 (Mitelman, 1998). Recently, we...
discovered by exome sequencing that as many as 70% of uterine leiomyomas harbour very specific somatic mutations in \textit{MED12} (Mäkinen \textit{et al}, 2011a). Strikingly, all mutations resided in exon 2, and the vast majority of them affected a single codon glutamine 44. The finding has subsequently been validated in other populations (Mäkinen \textit{et al}, 2011b; Je \textit{et al}, 2012; Markowski \textit{et al}, 2012; McGuire \textit{et al}, 2012). \textit{Mediator complex subunit 12} had not been implicated in human tumorigenesis before identification of specific exon 2 mutations in uterine leiomyomas. High mutation frequency and the proteins’ key role in transcriptional regulation prompted us to study the genes role in other tumour types. We collected a comprehensive series of 1158 samples representing various tumour types that might harbour mutations in the gene. These include both benign and malignant mesenchymal tumours, oestrogen- and progesterone-dependent tumours, and haematological malignancies, as retroviral insertions in \textit{Med12} have been reported to participate in the development of leukaemias in murines (Dave \textit{et al}, 2009). We also included tumours associated with abnormal Wnt-signalling, as preliminary data indicated this well-known cancer-related pathway may be dysregulated in \textit{MED12} mutation-positive uterine leiomyomas (Mäkinen \textit{et al}, 2011a).

\section*{MATERIALS AND METHODS}

\subsection*{Subjects}

Altogether 1158 tumours from as many patients were included in the study. The sample series consisted of 286 mesenchymal tumours (uterine leiomyosarcomas, other sarcomas, gastrointestinal stromal tumours, extraterine leiomyomas, endometrial polyps, lipomas), 216 oestrogen- and progesterone-dependent tumours (ovarian and breast carcinomas), 264 haematological malignancies (acute myeloid leukaemias, acute lymphoid leukemias, and myeloproliferative neoplasms), and 392 colorectal cancers (CRCs) as representatives of tumours commonly showing abnormal Wnt-signalling. See Table 1 for more details on the whole sample set utilised in the study, and Supplementary Information and Supplementary Tables S1,2 for additional information on uterine leiomyosarcomas and extraterine leiomyomas. The study was approved by the ethics review board of the Hospital District of Helsinki and Uusimaa (HUS), Helsinki, Finland, and the appropriate research permissions were obtained from local ethics committees.

\subsection*{DNA extraction and \textit{MED12} exon 2 mutation screening}

Genomic DNA was extracted from archival formalin-fixed paraffin-embedded and fresh-frozen tissue samples with standard methods. \textit{Mediator complex subunit 12} exon 2 mutation status was determined by direct sequencing. Two different sets of primers were used in the study. See Supplementary Information for more details.

\section*{RESULTS}

Five \textit{MED12} exon 2 mutations were identified in 1158 tumour samples, three in uterine leiomyosarcomas (3/41; 7%) and two in colorectal tumours (2/392; 0.5%) (Supplementary Table S3). No mutations were observed in any other tumour type. Two \textit{MED12} mutations were detected in histopathologically confirmed early-onset (dg $\leq$ 45 years) uterine leiomyosarcomas; one affecting the codon 44 that is frequently mutated in uterine leiomyomas (c.130G $\rightarrow$ A, p.Gly44Ser) and the other inserting 21 nucleotides and leading to an in-frame transcript (c.115_116ins21, p.Ala38_Leu39ins7). Corresponding normal DNA was available from these patients, and the somatic origin of the mutations was confirmed (Supplementary Figure S1). The third mutation was a three nucleotide deletion also resulting in an in-frame transcript (c.104_106delAAC, p.Glu35_Leu36delinsVal). This mutation was identified in a soft-tissue sarcoma sample, which was further diagnosed as a metastasis of uterine leiomyosarcoma. Unfortunately, normal DNA from this patient was not available for this study, and the somatic origin of this mutation could not be confirmed. It is likely, however, that this mutation is also somatic as it is located in a highly conserved area of the protein affecting the codon 36, which is the second most common mutational hotspot observed in uterine leiomyomas. Furthermore, no germ-line changes have been observed at this site in our own studies or reported in any published studies or in the databases. The fourth mutation (c.130G $\rightarrow$ T, p.Gly44Cys), again hitting the hotspot codon 44, was identified in one CRC sample. The female patient had been diagnosed with a Dukes B/grade II/microsatellite stable tumour in the sigmoid colon at the age of 78 years. A variant heterozygous for this mutation was detected in the sigmoid tumour sample (c.130G $\rightarrow$ T, p.Gly44Cys), in addition to the Dukes B stage tumour sample. The third mutation was a nonsense mutation (c.325C $\rightarrow$ T, p.Ala109X), identified in two additional CRC samples. The fourth mutation was a frameshift insertion (c.213_215delCTC, p.Ile72_Thr74delinsValSer), identified in one additional CRC sample.

\subsection*{Abnormal Wnt-signalling associated with MED12 mutations}

\begin{table}[h!]
\centering
\begin{tabular}{|l|c|c|c|}
\hline
\textbf{Tumour type} & \textbf{N} & \textbf{Sample type} & \textbf{Samples from} \\
\hline
Mesenchymal & & & \\
Uterine leiomyosarcoma & 39 & FFPE & PH/CFCH \\
Early onset (dg $\leq$ 45 years) & 27 & & PH \\
Unselected & 12 & & CFCH \\
Sarcoma & 104 & Fresh frozen & PH \\
Soft tissue sarcoma (including two ULMS) & 83 & & \\
Bone sarcoma & 21 & & \\
Gastrointestinal stromal tumour & 12 & FFPE & CFCH \\
Extraterine leiomyoma & 42 & FFPE & CFCH/PH \\
Endometrial polyp & 54 & FFPE & PH \\
Lipoma & 35 & FFPE & CFCH \\
Oestrogen-progesterone dependent & & & \\
Ovarian carcinoma & 122 & FFPE/fresh frozen & PH \\
Clear cell & 39 & & \\
Serous & 44 & & \\
Mucinous & 10 & & \\
Endometrioid & 10 & & \\
NOS & 19 & & \\
Breast cancer & 94 & Fresh frozen & OGH/PH \\
Ductal & 68 & & \\
Lobular & 14 & & \\
Medullary & 4 & & \\
Other & 8 & & \\
\hline
\end{tabular}
\caption{Tumours included in the \textit{MED12} exon 2 mutation screening data.}
\end{table}

Abbreviations: AAUH = Department of Hematology at Aarhus University Hospital; CFCH = Central Finland Central Hospital; FCH = Finnish Central Hospitals; FFPE = formalin-fixed paraffin-embedded; MSKCC = Memorial Sloan-Kettering Cancer Center; NOS = not otherwise specified; OGH = Department of Obstetrics and Gynecology at Helsinki University Central Hospital; PH = Department of Pathology at Helsinki University Central Hospital; ULMS = uterine leiomyosarcoma. * T-cell origin.
Figure 1 Mutations in MED12 exon 2. The whole MED12 exon 2 with the amino acids and codon numbers is shown at the top, and multispecies alignment of the regions with the detected mutations is shown below. Mutations observed in uterine leiomyosarcoma and CRC samples are marked with black and red, respectively. Mutations G44C and G44V in ULMS were reported by Pérot et al (2012). Mutation G44C in CRC was observed in this study and also in the study by The Cancer Genome Atlas Network (2012). Mutation D34Y in CRC has been reported by Je et al, 2011a; Markowski et al, 2010). The charge of amino acids is marked: small non-polar, magenta ¼ positively charged; small positively charged, red = negatively charged, green = hydrophobic, yellow = small non-polar; magenta = polar; blue = positively charged.

DISCUSSION

Our recent study revealed very specific mutations in MED12 exon 2 in as many as 70% of uterine leiomyomas (Mäkinen et al, 2011a). This study implicated, for the first time, a role for MED12 in human tumorigenesis. To analyse whether similar mutations can be found in other tumour types, we collected a broad spectrum of samples for the MED12 exon 2 mutation analyses.

Uterine leiomyomas originate from the smooth muscle cells and are thus of mesenchymal origin. Similar karyotypic changes that have been observed in uterine leiomyomas have also been seen in other benign mesenchymal tumours, such as extraterine leiomyomas, endometrial polyps, and lipomas (Tallini et al, 2000). We therefore hypothesised that these tumours might also harbour mutations in MED12. We screened altogether 131 benign mesenchymal tumours, but no mutations were identified. Similar results were recently reported by Markowski et al (2012), who found only one mutation in a single endometrial polyp and no mutations in the lipomas. Of specific note is that none of the 42 extraterine leiomyoma samples analysed in this study harboured MED12 mutations.

Altogether 155 malignant mesenchymal tumours were analysed for MED12 exon 2 mutations. Three mutations were observed, two in early-onset uterine leiomyosarcomas, and one in a metastasis of a uterine leiomyosarcoma (3/41; 7% of uterine leiomyosarcomas studied). This finding is in line with the results of a recent study by Pérot et al (2012), where MED12 mutations were reported in 2/10 (20%) uterine leiomyosarcomas and 1/9 (11%) smooth muscle tumour of uncertain malignant potential, respectively. Highly aggressive and malignant uterine leiomyosarcomas are not generally considered to develop from benign leiomyomas. The observed MED12 mutations are probably not the driving force behind the malignant transformation, but rather indicate that these tumours have developed from leiomyoma precursors. Indeed, it has also previously been suggested that a small subgroup of leiomyomas may actually develop into malignancy (Christacas et al, 2006). Would this be the case, identification of molecular markers that could be used in detecting such leiomyomas would be of great clinical importance as in most cases the leiomyosarcoma diagnosis is only made at surgery and many patients present with an advanced disease. In this study, no mutations were found in other sarcomas or in gastrointestinal stromal tumours. Overall, the low frequency of MED12 exon 2 mutations in various mesenchymal tumours suggests that the high mutation frequency observed in uterine leiomyomas is not a common feature for all mesenchymal tumours.

Development and growth of uterine leiomyomas are dependent on oestrogen and progesterone. Lesions show increased expression of oestrogen and progesterone receptors, and enhanced response to oestrogen stimulation compared with normal myometrial cells has been observed. Progesterone has also been reported to increase mitotic activity and regulate cell proliferation in uterine leiomyoma cells (Parker, 2007). To elucidate whether MED12 is involved in the tumorigenesis of other oestrogen- and progesterone-dependent tumours, we screened breast and ovarian cancer samples representing different histological subtypes for MED12 exon 2 mutations. None of the tumours harboured mutations, indicating that aberrant hormonal function is not the underlying cause, at least alone, for MED12 mutations in uterine leiomyomas.

Mediator complex subunit 12 interacts with β-catenin, and it has been identified as an important transducer of canonical Wnt/β-catenin signalling (Kim et al, 2006; Rocha et al, 2010). The preliminary results by us and Markowski et al imply that this signalling pathway may be altered in MED12 mutation-positive uterine leiomyomas (Mäkinen et al, 2011a; Markowski et al, 2012).
Dysregulation of Wnt/β-catenin pathway is involved in the development of many tumour types, including CRC (Polakis, 2000). Here, we identified two MED12 exon 2 mutations in altogether 392 CRC samples analysed. Similar results were recently reported by Je et al and The Cancer Genome Atlas Network, both of whom found one MED12 exon 2 mutation in 389 (0.3%) and 224 (0.4%) CRC samples, respectively (Je et al, 2012; The Cancer Genome Atlas Network, 2012). Although these mutations may have occurred just by chance, these findings suggest that specific MED12 exon 2 mutations may also be involved, albeit rarely, in the development of colorectal tumours.

Leukaemias have been shown to develop in murines with retroviral insertions in Med12 (Dave et al, 2009). A role for the CDK8 module/MED12 in hematopoiesis has also been suggested in Drosophila and zebrafish, respectively (Gobert et al, 2010; Keightley et al, 2011). High MED12 expression level has been observed in acute myeloid leukaemia and acute lymphoid leukaemia compared with other tumour types in the GeneSapiens database (http://www.genesapiens.org) (Kilpinen et al., 2008). In line with a previous study by Je et al, no MED12 exon 2 mutations in any haematological malignancies were detected (Je et al., 2012).

Taken together, screening of 1158 samples representing various tumour types revealed five MED12 exon 2 mutations; three in uterine leiomyosarcomas and two in CRC samples. Three mutations in the confirmed uterine leiomyosarcomas indicate that these tumours may have developed through a leiomyoma precursor. Supported by the observations by Je et al and The Cancer Genome Atlas Network, we also suggest that MED12 exon 2 mutations may contribute, albeit rarely, to CRC tumorigenesis (Je et al, 2012; The Cancer Genome Atlas Network, 2012).

Interestingly, Barbieri et al recently reported recurrent MED12 mutations affecting codon 1224 in 5 out of 111 (4.5%) prostate adenocarcinomas studied (Barbieri et al, 2012). It remains to be seen whether additional mutations in other parts of this large gene have a role in the development of various tumour types. The high MED12 exon 2 mutation frequency observed in uterine leiomyomas seem to associate with the location of the tumours in the uterus and also with their benign nature. The mechanistic details and the affected molecular pathways through which these extremely specific mutations promote tumorigenesis need to be unravelled at the molecular level utilising, for example, gene expression analyses, mouse models, and in vitro functional experiments. It is likely they alter a very specific function of the MED12 protein providing the cells with a growth advantage especially in the uterus.

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Supplementary Information accompanies the paper on British Journal of Cancer website (http://www.nature.com/bjc)

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MED12 mutations in various tumour types

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