Neuroblastoma is the most frequently occurring extracranial tumour type in children. It arises from the undifferentiated neural crest derived cells destined to become the sympathetic nervous system, and primary tumours typically occur in the adrenal medulla and paraspinal location in the abdomen or chest. At diagnosis, most children of >1 year of age have metastases, commonly in lymph nodes, bones, or bone marrow. However, in addition to potential lethal progression, neuroblastomas occasionally mature into benign ganglioneurotomas or spontaneously regress, even without treatment.1,2

Several acquired genetic changes have been described in neuroblastoma, the most frequent being MYCN oncogene amplification, 1p deletion, and 17q amplification.3 These alterations have been associated with aggressive forms of the disease; MYCN amplification in particular is used as a prognostic marker. In addition, chromosome number changes, translocations, and deletions in several other parts of the genome have been identified, but the significance of these changes needs further clarification.

A small subset of neuroblastoma cases have a family history of the disease and are diagnosed at a younger age with multifocal primary tumours.4 Hence Knudson and Strong postulated that the two hit model of cancer initiation could be applied to neuroblastoma, and that the mode of inheritance was consistent with autosomal dominant Mendelian pattern with incomplete penetrance.

Some linkage studies have been performed on familial neuroblastomas, and linkage to 4p16 and 16p12-13 has been suggested in families from Europe and North America, respectively.5,6 However, the chromosome 16p region was tested for linkage with negative results in Italian and British families.5,7 In addition, the known candidate neuroblastoma loci that are frequently altered sporadically have been excluded in some neuroblastoma families.5,7 Thus, despite extensive studies into neuroblastoma susceptibility, the putative predisposing genetic changes have remained unidentified, and additional analyses are required to further elucidate the mechanisms behind hereditary neuroblastoma development.

We report the genetic analyses of a Finnish girl who was diagnosed with neuroblastoma at the age of 2 years and 10 months. At diagnosis, she had advanced stage neuroblastoma, but with extensive therapy, she was cured of the disease. She was subsequently diagnosed with a psychomotor retardation/multiple congenital anomaly syndrome, Smith-Magenis syndrome (SMS), which was confirmed by karyotyping; the patient displayed a 17p11.2 germine deletion, characteristic of this syndrome. Because of the possible association of the neuroblastoma and the germine deletion, 17p11.2 was further evaluated in the patient’s normal tissue DNA, and in sporadic neuroblastomas and neuroblastoma cell lines.

We report the genetic analyses of a Finnish girl who was diagnosed with an advanced stage neuroblastoma at the age of 34 months. The patient was also diagnosed with Smith-Magenis syndrome at 9 years of age, and a germine deletion in 17p11.2 was detected as the underlying cause. Because of the possible association of the neuroblastoma and the germine deletion, 17p11.2 was further evaluated in the patient’s normal tissue DNA, and in sporadic neuroblastomas and neuroblastoma cell lines.

Using microsatellite marker analysis in the patient’s normal tissue DNA, the 17p11.2 deletion was found to span 4.2 Mb between markers D17S1837 and D17S842. Altogether, 11 sporadic neuroblastomas were analysed for loss of heterozygosity in the deleted region, but no allelic imbalance was detected. No other copy number changes were detected in the patient’s normal tissue DNA by array comparative genomic hybridization.

Data from serial analysis of gene expression on neuroblastoma cell lines revealed that five genes in the deleted 17p11.2 region might have a role in neuroblastoma development. Of the identified genes, Ubb and Usp22 are involved in protein degradation, while Tom1l2, Mfap4, and Prpsap2 have functions related to protein trafficking, cell adhesion, and synthesis of nucleotides, respectively.

Studying a more extensive series of neuroblastomas can help assess the importance of the affected region and the candidate genes.

METHODS

The primary tumour (stage IV) was in the left adrenal medulla and dense metastasis in the bone marrow was detected. Amplification at the MYCN locus was detected by

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**Key points**

- Neuroblastoma is the most common solid tumour type in children, and is characterised by diverse clinical behaviour and multiple genetic alterations. Despite numerous studies on the molecular background of neuroblastoma, the causative changes have not been fully characterised, making additional analyses necessary.
- We report the genetic analyses of a Finnish girl who was diagnosed with an advanced stage neuroblastoma at the age of 34 months. The patient was also diagnosed with Smith-Magenis syndrome at 9 years of age, and a germine deletion in 17p11.2 was detected as the underlying cause. Because of the possible association of the neuroblastoma and the germine deletion, 17p11.2 was further evaluated in the patient’s normal tissue DNA, and in sporadic neuroblastomas and neuroblastoma cell lines.
- Using microsatellite marker analysis in the patient’s normal tissue DNA, the 17p11.2 deletion was found to span 4.2 Mb between markers D17S1837 and D17S842. Altogether, 11 sporadic neuroblastomas were analysed for loss of heterozygosity in the deleted region, but no allelic imbalance was detected. No other copy number changes were detected in the patient’s normal tissue DNA by array comparative genomic hybridization.
- Data from serial analysis of gene expression on neuroblastoma cell lines revealed that five genes in the deleted 17p11.2 region might have a role in neuroblastoma development. Of the identified genes, Ubb and Usp22 are involved in protein degradation, while Tom1l2, Mfap4, and Prpsap2 have functions related to protein trafficking, cell adhesion, and synthesis of nucleotides, respectively.
- Studying a more extensive series of neuroblastomas can help assess the importance of the affected region and the candidate genes.
fluorescence in situ hybridisation (FISH). With extensive
treatment including surgery, chemotherapy, radiotherapy,
and stem cell transfection, she was cured and has remained
disease free since, being 11 years of age at present. At the age
of 9 years, the patient was diagnosed with SMS, charac-
terised by psychomotor retardation, craniofacial dysmorph-
ism, behavioural abnormalities such as aggressive and self
destructive behaviour, and multiple organ anomalies, includ-
ing cardiovascular, genitourinary, and ophthalmic anom-
alias.10 She had normal early development, but strabismus
was noted at 6 months of age and speech delay at the time of
neuroblastoma diagnosis. Brain MRI at the age of 3 years
showed bilateral subependymal nodular heterotopia, and at
5 years of age mild psychomotor retardation was obvious.
The patient has major behavioural and sleep disturbances,
and shows typical dysmorphic features of SMS, including
brachycephaly, flat mid-face, prominent jaw, and large
mouth. Her parents and brother are healthy, but her sister
has been diagnosed with a heart malformation (atrioventric-
tular septal defect).

To confirm the SMS diagnosis, the patient’s lymphocytes
were screened for chromosomal aberrations with 550 band
accuracy. The karyotype was normal apart from a deletion in
chromosome 17p11.2. To complete the SMS diagnostic
procedures, the result was confirmed by FISH.

To fine map the deleted region, microsatellite markers
spanning 17p11.2 were chosen based on Ensembl database
(http://www.ensembl.org/) or designed based on the
sequence data. We performed microsatellite marker analysis
on the normal tissue DNA of the patient and the parents. PCR
conditions and primer sequences are available upon request.
PCR products were run on an ABI Prism 377 DNA sequencer
(Applied Biosystems, Branchburg, NJ, USA) according to the
manufacturer’s instructions, and the collected data were
analysed by GeneScan 3.1 and Genotyper 2.5 software
(Applied Biosystems).

To further assess the deleted region we analysed the
patient’s normal tissue DNA with array CGH. The hybridisa-
tions (using an Agilent Human 1 cDNA Microarray kit) were
performed by the Biomedicum Biochip Center, Helsinki,
Finland, according to the procedures of Monni et al.11

To identify those 17p11.2 genes that could have a role in
known neuroblastoma differentiation pathways, neuroblas-
toma SAGE data was scrutinised. More specifically, we
studied the pathways of MYCN and Meis1, which are
amplified in a subset of neuroblastomas,12 13 and of TrkA,
the expression of which is associated with neuroblastomas
with good prognosis.14 The SAGE data was acquired by
transfecting neuroblastoma cell lines SH-EP, SJ-NB8, and
SH-SY5Y with MYCN, Meis1, or TrkA, respectively. The
downstream pathways of the transfected genes were ana-
lysed by high throughput mRNA expression profiling. A set of
SAGE libraries was constructed from the transfected and
untransfected cells, and the libraries were analysed for
differentially expressed genes.15 16

In addition, we analysed 11 sporadic neuroblastomas and
corresponding normal tissue samples for LOH using micro-
satellite markers in the deleted region.

RESULTS

Chromosomal analyses on the patient’s lymphocytes
performed in a diagnostic setting showed a deletion in 17p11.2
(46,XX,del(17)(p11.2p11.2)). The finding was confirmed by
FISH with an FLI1 probe (del(17)(p11.2p11.2)
(MDCR4,FLI1–)). We fine mapped the affected region with
microsatellite marker analysis, and the deletion was shown to
lie between markers D17S1857 and D17S842. These markers
delineate the deletion, as they displayed heterozygosity in the
patient’s normal tissue DNA.

Altogether, 12 markers were examined between these two
markers, five of which were informative and showed a
deletion of the other allele (fig 1). The deleted interval
corresponds to a 4.2 Mb distance (Ensembl, 22nd July 2004
update). Genes spanning the deleted region are presented in
table 1. According to microsatellite analysis, there were no
deletions in the DNA of the patient’s parents, and the deleted
allele was maternal.

The normal tissue DNA of the patient was analysed by
array CGH. The results correlated with the microsatellite
marker data in that the deleted region contained genes with
nearly 50% intensity reduction. According to the array CGH,
there were no other clear areas with copy number changes in
the patient’s normal tissue DNA, a finding compatible with
the karyotyping result. Most of the successfully hybridised
genes within the deletion have unknown functions.

The affected 17p11.2 region harbours at least 83 genes
(table 1). To identify those genes that could have a role in
neuroblastoma differentiation, we analysed MYCN, Meis1,
and TrkA regulated gene expression in three neuroblastoma cell
lines by SAGE. This approach identified a few hundred genes
in the downstream pathways of MYCN, Meis1, and TrkA. In
the 17p11.2 region, five genes displayed changes in their
expression patterns. MYCN decreased the expression of Ubb
and Tomil2, whereas Prnpap2, Mfap4, and Usp22 were down-
regulated by Meis1. Mfap4 expression was also upregulated by
TrkA (table 2).

We also studied 11 sporadic normal/tumour tissue neuro-
blastoma samples for LOH by microsatellite marker analysis.
We performed analysis on four markers in the deleted region
but none of the samples showed allelic imbalance at these
markers according to two independent viewers. At least two,
typically three, markers were informative in each normal/
tumour sample pair.
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DISCUSSION
Neuroblastoma is a complex disease with diverse clinical behaviour and largely unknown aetiology. Linkage studies in neuroblastoma families have suggested the existence of predisposing gene(s) in chromosomes 4 and 16, but other studies have produced negative results in chromosome 16 and some of the regions commonly altered in neuroblastomas. This suggests that multiple genes could be involved in neuroblastoma development and hence linkage found in some populations might not be detected in other populations. The observation of several deleted regions in neuroblastomas without gene identification raises the possibility that haploinsufficiency might also be involved. Thus, the genetic mechanisms involved in neuroblastoma development need to be clarified further, and additional analyses on neuroblastomas are of great importance as they can lead to better understanding, diagnosis, and management of the disease.

In the present work, we performed genetic analyses on a young patient with advanced stage neuroblastoma and metastasis of the disease. The patient was also diagnosed with SMS. According to prometaphase chromosome analysis, there was a 17p11.2 chromosome deletion in the normal tissue DNA. The deleted region was defined with microsatellite marker analysis and was seen to lie between markers D17S1857 and D17S842.

In neuroblastoma, 17p deletions are rare. However, chromosome 17p11.2 deletions have been frequently observed, for example in childhood primitive neuroectodermal tumours, where the commonly deleted region overlaps with the critical region deleted also in SMS. Although 17p11.2 deletion is a characteristic aberration in SMS patients, there are rare cases where 17p11.2 deletions have not been detected. These cases are phenotypically consistent with SMS, but do not display some of the SMS associated features, such as heart defects or short stature. Recently, three such patients were identified with truncating mutations in \textit{Rai1}, which was later cloned from a neuroblastoma cell line. \textit{Rai1} has been associated with neuronal differentiation in mouse studies. Thus \textit{Rai1} could be responsible for the behavioural, neurological, otolaryngological, and craniofacial anomalies of SMS, and the other features of this syndrome could result from hemizygosity of other genes in the 17p11.2 region.

To our knowledge, there have been no reports of tumour predisposition associated with SMS, although the syndrome is characterised by variable phenotypic features. This argues

\begin{table}[h]
\begin{center}
\begin{tabular}{|l|l|l|l|l|l|l|l|}
\hline
Gene & Start position, bp & \textbf{SH-EP} & \textbf{SJ-NB8} & \textbf{SH-SY5Y} & \textbf{MYCN} & \textbf{Meis1} & \textbf{TrkA} \\
\hline
\textit{Ubb} & 16 484 927 & 23 & 12 & 15 & 12 & 17 & 13 \\
\textit{Tom1/2} & 17 950 706 & 55 & 29 & 70 & 70 & 74 & 61 \\
\textit{Prpsap2} & 18 962 058 & 9 & 0 & 0 & 0 & 0 & 0 \\
\textit{Mtap4} & 19 448 786 & 2 & 15 & 12 & 5 & 0 & 21 \\
\textit{Usp22} & 21 068 373 & 0 & 9 & 6 & 1 & 4 & 4 \\
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\textbf{Total} & & 22 & 12 & 11 & 1 & 11 & 4 \\
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\caption{\textbf{MYCN}, \textit{Meis1}, or \textit{TrkA} regulated gene expression in SH-EP, SJ-NB8, and SH-SY5Y neuroblastoma cell lines.}
\end{table}
against the existence of important tumour suppressors in the SMS commonly deleted region. The phenotypic variability of SMS can perhaps be partly explained by the differences in the 17p11.2 deletion size. The deletion size can vary because of the occurrence of alternative low copy repeats (LCRs) in the 17p11.2 region. LCRs can act as substrates for non-allelic homologous recombination that results in deletion, duplication, or inversion of the genomic segments flanked by the LCRs. The deletion detected in our neuroblastoma patient is larger than those typically seen in SMS patients. Thus the genes locating closer to the deletion breakpoints, rather than the SMS commonly deleted region, might be of particular interest for neuroblastoma predisposition.

We analysed the deleted 17p11.2 region further with array CGH and SAGE. The array CGH data correlated well with the results obtained from the microsatellite analysis and no other clear copy number changes were detected in the patient’s normal tissue DNA. However, most genes within the deleted region have unknown functions. SAGE data was used to identify any 17p11.2 genes that could be involved in neuroblastoma development. The downstream targets of MYCN, Meis1, and TrkA pathways were examined in three neuroblastoma cell lines. MYCN and Meis1 are oncogenes, and their downregulated targets might be associated with differentiation. Haploinsufficiency of these target genes due to the deletion could potentially block a differentiation step and thereby promote pathogenesis of neuroblastoma. TrkA expression is associated with good prognosis of neuroblastoma, and may therefore upregulate genes with differentiation potential. Similarly, a deletion of the upregulated genes could block differentiation.

The SAGE analyses of the neuroblastoma pathways identified five genes in the deleted region that could have a role in neuroblastoma development. MYCN was shown to regulate the expression of Ubb and TomIL2, which are involved in protein degradation and trafficking, respectively. An aberrant form of Ubb has also been detected in the cerebral cortex of Alzheimer’s and Down’s syndrome patients. Other candidate genes downregulated by Meis1 or upregulated by TrkA were Mfap4, Usp22, and Prpsap2, which have functions related to cell adhesion, protein degradation, and synthesis of nucleotides and histidine, respectively.

Our SAGE data suggest that these five genes could have a role in the previously identified neuroblastoma pathways, and further analyses of their roles in neuroblastoma may therefore be of interest.

In addition to the genes identified by SAGE, one of the possible candidates within the 17p11.2 region is LGL1, a human homologue of the Drosophila lethal giant larvae gene, which is associated with neuroblast development in Drosophila. However, LGL1 was not represented in the array CGH chip or SAGE.

In this paper, we report a germline 17p11.2 deletion in a neuroblastoma patient who had advanced stage and metastatic disease but was cured with extensive treatment. NO LOH of the 17p11.2 region was found in a limited set of sporadic neuroblastomas. As the deletion might be a random event with no tumorigenic implications, additional samples of different clinical types need to be analysed to obtain more detailed information on the possible importance of the affected region in neuroblastoma development. Although some attractive candidate genes reside in the deleted region according to our array CGH analysis and SAGE data, genes with unknown or less attractive functions also have to be considered. Genotyping a more extensive neuroblastoma sample set might aid in confirming the putative association between 17p11.2 and neuroblastoma, and further fine map the relevant region to form solid basis for candidate gene analyses by sequencing and other methods.

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A 17p11.2 germline deletion in a patient with Smith-Magenis syndrome and neuroblastoma

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