Gain of chromosome arm 17q is associated with unfavourable prognosis in neuroblastoma, but does not involve mutations in the somatostatin receptor 2 (SSTR2) gene at 17q24

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Summary Deletion of chromosome arm 1p and amplification of the MYCN oncogene are well-recognized genetic alterations in neuroblastoma cells. Recently, another alteration has been reported; gain of the distal part of chromosome arm 17q. In this study 48 neuroblastoma tumours were successfully analysed for 17q status in relation to known genetic alterations. Chromosome 17 status was detected by fluorescence in situ hybridization (FISH). Thirty-one of the 48 neuroblastosomas (65%) showed 17q gain, and this was significantly associated with poor prognosis. As previously reported, 17q gain was significantly associated with metastatic stage 4 neuroblastoma and observed in children with low-stage tumours (stage 1, 2, 3 and 4S), with a survival probability of 100% at 5 years from diagnosis for children with tumours showing no 17q gain compared to 52.5% for those showing 17q gain (P = 0.0021). This suggests that 17q gain as a prognostic factor plays a more crucial role in low-stage tumours. Expression of the somatostatin receptor 2 (SSTR2), localized in chromosome region 17q24, has in previous studies been shown to be positively related to survival in neuroblastoma. A point mutation in the SSTR2 gene has earlier been reported in a human small-cell lung cancer. In this study, mutation screening of the SSTR2 gene in 43 neuroblastoma tumours was carried out with polymerase chain reaction-based single-stranded conformation polymorphism/heteroduplex (SSCP/HD) and DNA sequencing, and none of the tumours showed any aberrations in the SSTR2 gene. These data suggest that mutations in the SSTR2 gene are uncommon in neuroblastoma tumours and do not correlate with either the 17q gain often seen or the reason some tumours do not express SSTR2 receptors. Overall, this study indicates that gain of chromosome arm 17q is the most frequently occurring genetic alteration, and that it is associated with established prognostic factors. © 1999 Cancer Research Campaign

Keywords: 17q; SSTR2; neuroblastoma

Neuroblastoma, a malignant tumour of the sympathetic nervous system, is the most common extracranial solid tumour of childhood (Gale et al, 1982). The clinical behaviour of neuroblastoma varies from spontaneous regression to malignant progression. It can also differentiate into a benign ganglioneuroma in some older patients. Generally, favourable outcome is associated with young age of diagnosis, but biological differences of the tumours in the age groups appear to be very important as well (reviewed in Brodeur, 1998).

A number of genetic alterations has been shown to be associated with poor prognosis, and these have been used as genetic markers of neuroblastoma. The two most important types of somatic abnormalities are deletion of the distal part of the short arm of chromosome 1 (1p), and amplification of the MYCN oncogene. Both MYCN amplification and 1p deletion are associated with rapid progression and poor prognosis (Seeger et al, 1985; Ambros et al, 1995; Caron et al, 1996). DNA content of neuroblastoma has been shown to be associated with prognosis as well. Tumours with increased DNA content (or ‘polyploid’ karyotype) is associated with a favourable outcome in infants with neuroblastoma (Look et al, 1991). Recently, focus has been directed towards a third karyotypic abnormality in neuroblastoma tumours, i.e. extra copies of the distal part of the long arm of 17 (17q gain). 17q gain is defined as a structural rearrangement of chromosome 17, which results in partial gain of 17q relative to 17p. This almost invariably involves a breakpoint in 17q12–21 with gain of the distal portion of the 17q arm (Lastowska et al, 1997a). Unbalanced translocation resulting in loss of distal 1p and gain of 17q has previously been identified by fluorescence in situ hybridization (FISH) in primary tumours and neuroblastoma cell lines (Caron et al, 1994; Van Roy et al, 1994). It was also demonstrated by Southern blot and cytogenetic analysis that the translocation very likely takes place in the S/G2 phase (Caron et al, 1994). More recently, comparative genomic hybridization (CGH) studies have shown that extra chromosome 17q material occurs in approximately 70–80% of primary tumours, either as gain of the whole chromosome 17 or the q arm alone (Plantaz et al, 1997; Lastowska et al, 1998; Vandsompele et al, 1998). Using FISH studies Meddebe et al (1996) and Lastowska...
et al (1997b) showed that 17q can translocate on to a number of chromosome regions other than 1p, and that such rearrangements also result in gain of 17q material. Meddeb et al (1996) reported that among translocations only 17% were (1;17) translocations, whereas the remainder involved various other chromosomes: chromosome 4, 5, 6, 9, 11, 12, 14, 17 and 19. Moreover, both groups found that 17q gain also showed correlation to poor prognosis. A third study showed that 17q gain is associated with all established indicators of poor prognosis; stage 4 disease, age above 1 year at diagnosis, 1p deletion, MYCN amplification and diploidy/tetraploidy (Lastowska et al, 1997a). Lastowska et al (1997a) and Caron et al (1996) also found that 17q gain was associated with poor outcome.

Somatostatin (SST; synonym name ‘somatotropin release inhibitory factor’, SRIF), a growth hormone inhibitory substance, is a multifunctional peptide that is distributed widely throughout the central nervous system (CNS) and peripheral tissues (reviewed in Bell et al, 1995; Patel et al, 1995). At cellular level, actions of SST is involved in many different processes, including cell proliferation (Patel et al, 1995). Recently, it was shown by radioimmunoassay that somatostatin in neuroblastoma is associated with differentiation to benign ganglioneuroma in vivo and favourable outcome in advanced tumours (Kogner et al, 1997).

The physiological actions of somatostatin are mediated by high-affinity receptors on the surface of responsive cells that are coupled by G proteins to a multiple effector system including adenyl cyclase, ion channels and tyrosine phosphatases. Five somatostatin receptors subtypes, SSTR 1–5, have been cloned (Yamada et al, 1992). The somatostatin receptor isoform 2 gene (SSTR2) is mapped to 17q24 and encodes a 369 amino acid membrane protein (Yamada et al, 1992). Recently, in vivo expression of SSTR2 in neuroblastoma tumours was shown to be correlated with young age at diagnosis, localized clinical stage and favourable outcome (Schilling et al, 1999). In another study, Sestini et al (1996) found that SSTR2 expression in vitro was negatively related to MYCN amplification and according to Kaplan–Meier analysis positively related to survival. Interestingly, Zhang and associates found a point mutation in the SSTR2 gene in human small-cell lung cancer cell line COR-L103 (Zhang et al, 1995). The mutation caused loss of the C-terminal amino acid residue number 182 of SSTR2.

The aims of this study were to investigate the occurrence of 17q gain in the patient material of the Swedish neuroblastoma tumour study group, and its relation to survival and poor prognostic factors such as MYCN amplification, 1p deletion and diploid/diploidy (Lastowska et al, 1997a). Lastowska et al (1997a) and Caron et al (1996) also found that 17q gain was associated with poor outcome.

**Materials and Methods**

**Patients**

Tumour samples were obtained from 48 children with neuroblastoma of all different stages (Table 1). The children were staged according to the International Neuroblastoma Staging System criteria (INSS, Brodeur et al, 1993). Tumour cell content of the samples was histologically assessed in adjacent tumour tissue to that used for DNA extraction. All tumour specimens were used for PCR-based DNA polymorphisms. The material was used for polymerase chain reaction (PCR)-based SSCP/HD detection of MYCN, 1p deletion and diploid/diploidy (Lastowska et al, 1997a). Lastowska et al (1997a) and Caron et al (1996) also found that 17q gain was associated with poor outcome.

| Patients | Stage | Sex | 1p-del | N-myc | 17q gain | Outcome | Survival |
|----------|-------|-----|--------|-------|----------|---------|----------|
| 84       | 1     | F   | –      | –     | –        | N       | 97+      |
| 124      | 1     | M   | nd     | –     | –        | N       | 61+      |
| 146      | 1     | F   | –      | –     | –        | N       | 80+      |
| 156      | 1     | M   | –      | –     | –        | N       | 75+      |
| 161      | 1     | F   | –      | –     | –        | N       | 68+      |
| 181      | 1     | F   | –      | –     | +        | N       | 47+      |
| 51       | 2A    | F   | –      | –     | –        | N       | 134+     |
| 121      | 2A    | M   | –      | +     | –        | D       | 96       |
| 177      | 2A    | M   | –      | –     | –        | N       | 13+      |
| St156    | 2A    | F   | –      | +     | –        | N       | 2+       |
| St124    | 2     | M   | +      | –     | +        | A       | 26+      |
| 127      | 2B    | F   | –      | –     | +        | N       | 87+      |
| 138      | 2B    | M   | –      | –     | +        | N       | 79+      |
| 125      | 4S    | M   | nd     | –     | –        | N       | 89+      |
| St142    | 4S    | M   | (+)    | +     | +        | D       | 0        |
| 69       | 3     | M   | –      | –     | +        | D       | 17       |
| 85       | 3     | F   | –      | –     | –        | N       | 98+      |
| 128      | 3     | M   | nd     | nd    | –        | N       | 89+      |
| 135      | 3     | M   | nd     | +     | –        | D       | 6        |
| 136      | 3     | F   | nd     | +     | –        | D       | 11       |
| 152      | 3     | F   | –      | –     | –        | N       | 74+      |
| 157      | 3     | M   | –      | –     | –        | DOC     | 0        |
| 187      | 3     | F   | –      | –     | +        | A       | 7+       |
| St99     | 3     | F   | +      | –     | +        | D       | 10       |
| St100    | 3     | F   | –      | –     | –        | N       | 47+      |
| St131    | 3     | M   | +      | +     | L        | L       |
| St164    | 3     | M   | +      | +     | A        | 7+       |
| 32       | 4     | M   | –      | –     | +        | D       | 12       |
| 41       | 4     | F   | –      | –     | –        | D       | 8        |
| 49       | 4     | M   | nd     | nd    | –        | D       | 16       |
| 55       | 4     | F   | +      | +     | –        | D       | 4        |
| 95       | 4     | F   | +      | +     | –        | D       | 15       |
| 106      | 4     | F   | +      | +     | –        | N       | 76+      |
| 107      | 4     | M   | –      | –     | +        | D       | 10       |
| 112      | 4     | M   | –      | –     | –        | D       | 18       |
| 114      | 4     | F   | –      | –     | (+)      | D       | 25       |
| 123      | 4     | F   | nd     | +     | –        | D       | 4        |
| 126      | 4     | M   | –      | +     | –        | D       | 8        |
| 155      | 4     | F   | –      | +     | –        | D       | 19       |
| 163      | 4     | M   | +      | –     | –        | D       | 10       |
| 174      | 4     | F   | +      | +     | –        | D       | 6        |
| St102    | 4     | M   | +      | +     | –        | D       | 11       |
| St116    | 4     | F   | –      | –     | –        | A       | 32+      |
| St118    | 4     | M   | –      | –     | +        | A       | 24+      |
| St119    | 4     | M   | +      | –     | (+)      | A       | 24+      |
| St126    | 4     | F   | +      | +     | –        | A       | 25+      |
| St130    | 4     | F   | (+)    | +     | –        | D       | 10       |
| St153    | 4     | M   | nd     | –     | –        | L       |

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FISH analysis, and 43 from which DNA had been extracted were used for polymerase chain reaction (PCR)-based SSCP/HD detection. Of these, 32 were sequenced for the SSTR2 gene. In previous studies (Martinsson et al, 1995, 1997, and unpublished data), MYCN amplification and 1p deletion have been detected for most of the patients included in this study using FISH analysis and PCR-based DNA polymorphisms.
PCR-amplification

Forward (F) and reverse (R) primers for the SSTR2 gene (17q24) and marker D17S796 (17p) were synthesized using an ABI Applied Biosystem 392 DNA/RNA Synthesizer. SSTR2 exon 1, corresponding to the complete SSTR2 isoform 2a and approximately 94% of isoform 2b, and the alternatively spliced exon 2, corresponding to the remainder of SSTR2 isoform 2b (Patel et al., 1993), was amplified in five pieces using primers according to Table 2. Primer sequences for SSTR2 were selected using the DNASTAR primer select software (Lasergene, Madison, WI, USA) from the published cDNA sequences (GenBank accession numbers M81830 and L13033). Primers for D17S796 were from Dib et al. (1996). Amplifications were carried out in 20-μl volume containing 50–100 ng template DNA; 15 pmol of each primer; 10 mM Tris–HCl (pH 8.3); 30 mM potassium chloride; 1.5 mM magnesium chloride; 0.001% (w/v) gelatin; 4.4 nmol of each dATP, dCTP, dGTP, dTTP, and 0.25 U Taq DNA polymerase with an initial pre-warm at 37°C. SSTR2–4 was amplified in 30 cycles of 30–45 s at 94°C, 30–45 s at 58°C and 60 s at 72°C. Following the last cycle, an additional extension step was performed for 5 min at 72°C. SSTR2–4 was amplified in 30 μl volume containing 2.5 U Taq DNA polymerase with an initial incubation at 95°C for 5 min.

Cytogenetic preparations

Touch prepared imprint slides from primary neuroblastoma tumours were subjected to standard procedures of hypotonic treatment (0.3% sodium chloride) for 10 min and fixation in increasing concentrations of ethanol:acetic acid (vol. 3:1) solution.

Isolation of bacterial artificial chromosomes and labelling of probes for FISH

The human bacterial artificial chromosomes (BAC) DNA pool library, purchased from Research Genetics Inc. (Huntsville, AL, USA), was screened with PCR-assays using primers for marker D17S796 (17p) and primers for the SSTR2 gene (17q24) respectively (Table 2). The BAC-DNA was extracted and purified using QIAGEN Plasmid Purification kit. The 17q-BAC (146-G1) was labelled with FluoroX-dCTP with nick translation according to FluoroLink Cy3 Nick Translation Kit (Amersham Life Science). The labelled BAC-DNAs were used as FISH probes on touch prepared imprint slides.

Fluorescence in situ hybridization

The probes were used for Cy3 labelled BAC 43-C7 (17q24, giving a red signal), FluoroX labelled marker BAC 146-G1 (17p, giving a green signal), and digoxigenin/FITC-labelled p53 (17p13.1, giving a green signal) from Oncor. The probes were hybridized to metaphase chromosome control slides and to interphase slides from primary NB tumours. Slides were dehydrated in ethanol series, and denatured in sodium hydroxide (NaOH) solution (0.6% NaOH, 70% ethanol). The interphase slides were pre-washed in 70% acetic acid for 30 s, and dehydrated in both ethanol and acetone. BAC-probes were denatured for 10 min at 73°C in hybridization buffer (50% formamide, 10% dextran sulphate, 2× SSC (standard saline citrate), final pH 7.0) and pre-hybridized in the presence of a 50-fold excess of Cot-1 DNA (Life Technologies) for 2 h at 37°C. The 17p-digoxigenin probe was pre-warmed at 37°C for 5 min. Ten microlitres of each probe was applied to slides in mixtures and hybridization was performed under a 25 × 25 mm coverslip in a moist chamber at 37°C overnight.

After hybridization, slides were washed in 2× SSC at 50°C. Slides hybridized with 17p-digoxigenin probe were immuno-chemically stained with fluorescein isothiocyanate (FITC)-conjugated anti-digoxigenin antibody (Oncor) under a coverslip in a moist chamber at 37°C for 20 min. DNA was stained in 0.25 μg ml⁻¹ 4,6-Diamidino-2-Phenylindole (DAPI, Sigma) in Na₂HPO₄-buffer, pH 7.0, and an anti-fade solution containing 2% 1,4 diazabicyclo(2,2,2) octane (DABCO, Sigma), 69% glycerol, 2 mM Tris–HCl, pH 8.0, and 0.9 mg ml⁻¹ p-phenylenediamine (PPD, Sigma) was applied. The preparations were examined with a Zeiss Axioshot microscope with appropriate filters, photographed with a computer-driven IMAC-CCD colour camera and modified with the Meta system (Meta systems, Hard & Software GmbH, D68804 Altusheim, Germany).

SSCP/HD

The SSCP/HD electrophoreses were run on 20% homogeneous Phast gels with buffer system of native strips in Tris–tricine (0.2 M Tris, 0.2 M tricine) at 15°C, 400 V, 5.0 mA, 1.0 W for 250 Ahv on a Phast system (Pharmacia Biotech). The Phast gels were pre-run.
Role of chromosome arm 17q in neuroblastoma

Neuroblastoma is an extremely heterogeneous disease, and a number of genetic and cytogenetic alterations have shown to associate with prognosis. In the present study, FISH was used to study status of chromosome 17q in 48 neuroblastoma tumours. 17q gain

DISCUSSION

Neuroblastoma is an extremely heterogeneous disease, and a number of genetic and cytogenetic alterations have shown to associate with prognosis. In the present study, FISH was used to study status of chromosome 17q in 48 neuroblastoma tumours. 17q gain
was detected in 65% of the neuroblastoma tumours. Moreover, 17q gain was found to be associated with poor prognostic factors such as deletion of chromosome arm 1p and amplification of the MYCN oncogene. These findings are supported by earlier studies (Lastowska et al, 1997a; Plantaz et al, 1997). The association between 1p deletion and 17q gain is not surprising since physical
The connection between these chromosomes has been seen in the form of unbalanced translocations der(1)t(1p;17q) (Caron et al, 1994; Van Roy et al, 1994; Meddeb et al, 1996; Lastowska et al, 1997a, 1997b). These translocations result in loss of 1p and gain of 17q, and are thought to occur in the S/G2 phase of the cell cycle (Caron et al, 1994). In the present study, FISH was only carried out on interphase cells, and therefore the frequency of such translocation could not be investigated. The association between MYCN...
amplification and 17q gain is more difficult to explain. There are some few cases where MYCN HSRs are flanked by 17q material (Van Roy et al, 1994; Lastowska et al, 1997a). But such rearrangements are not generally seen in primary tumours, where MYCN amplifies mainly in the form of double minute chromosomes (Lastowska et al, 1997a). As found in the present study and in earlier reports, all these three alterations: 1p-deletion, MYCN amplification, and 17q gain, show strong association to each other. This gives rise to speculations whether they are structurally related in some kind of way. Like two earlier studies (Meddeb et al, 1996; Lastowska et al, 1997a) we also found that the number of 17q gain (31 out of 48 analysed neuroblastomas) exceeded the number of 1p deletions (14/40) and the number of MYCN amplifications (16/46). But not all of the 1p deletions and MYCN amplifications status were determined in this study, which has to be taken into account. Nevertheless, these results indicate that 1p deletion and MYCN amplification could be secondary events of 17q gain as a primary event.

In the present study most of the 17q gain tumours showed 1 additional signal of 17q (2+3), but 36% of the 17q gain tumours also showed two or more additional signals (2+4, 2+5) of 17q (Figure 1). This gave rise to questions about 17q gain being a dose-dependent feature. However, in this study no differences in survival probability between patients showing one additional 17q signal in relation to patients showing two or more additional 17q signals in the tumour specimens could be seen.

In the present study, five patients who died of disease had 17q gain without 1p deletion and MYCN amplification (cases 69, 32, 41, 107 and 114; Table 1), but there were also a number of patients surviving with no evidence of disease that showed 17q gain (e.g. cases 181, St156, 127, 138 and 106). However, from the data it is clear that children with tumours of all different stages showing 17q gain had a significantly worse outcome, 18 of 29 dead of disease versus three of 16 among those with tumours with no 17q additional material. Survival probability according to Kaplan–Meier was also better for those with no 17q gain, 75% at 5 years from diagnosis compared to 34% for those with 17q gain ($P = 0.0009$, Figure 2A). Remarkably, among children with low-stage tumours (stage 1, 2, 3 and 4S) only those showing 17q gain died of disease (six of six), whereas none of those showing no 17q gain died from disease ($P = 0.0021$, Figure 2B). In contrast, children with high-stage tumours (stage 4) showing 17q gain had no significantly worse outcome, 12 of 16 dead of disease versus three of four among those with tumours showing no 17q additional material. These results suggest that 17q gain as a prognostic factor plays a more crucial role in low-stage tumours, and that metastatic stage 4 tumours display many other adverse prognostic factors (1p-deletions, MYCN amplifications, etc.) which somehow surpass the effect of 17q gain. As seen in the Venn-diagram no low-stage tumour and only two of the high-stage tumours showed 1p-deletion or MYCN amplification without showing 17q gain as well (Figure 2B). This supports the hypothesis of 17q gain as a primary genetic event.

Two studies, one by in vivo detection with $^{111}$In-pentetreotide scintigraphy (Schilling et al, 1998) and one by in vitro detection with competitive reverse transcription PCR (RT-PCR) (Sestini et al., 1996), have shown that expression of SSTR2 in neuroblastoma tumours is positively related to survival and negatively related to poor prognosis. A point mutation in the SSTR2 gene, causing loss of 182 C-terminal amino acid residues of SSTR2, has earlier been detected in a human small-cell lung cancer carcinoma (Zhang et al, 1995). In the present study we wanted to investigate whether the low level of SSTR2 expression in unfavourable neuroblastomas is a primary genetic event as described for the point mutation in the SSTR2 gene in small-cell lung cancer. Screening of 43 neuroblastoma tumours for mutations in the SSTR2 gene was carried out with PCR-based SSCP/HD and sequencing. We found that all SSCP patterns were normal compared to the wild-types, and no mutations could be detected in the SSTR2 gene of the 32 successfully sequenced cases as a contrast to the reported SSTR2 gene mutation earlier detected in a colon cancer cell line (Zhang et al, 1995). This suggests that mutations in the SSTR2 gene is uncommon in neuroblastoma tumours and not related to the 17q gain often seen in these.

In conclusion, the neuroblastoma patients analysed in this study have a high incidence of 17q gain in agreement with what have been reported by other groups. 17q gain is associated with poor prognosis and with other prognostic factors. No mutations could be detected in the SSTR2 gene that explains its reported low expression in high-stage neuroblastoma.

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REFERENCES

Ambros PF, Ambros IM, Strehl S, Bauer S, Luegmayr A, Kavar H, Ladenstein R, Fink FM, Hoerer E, Printz G, et al (1995) Regression and progression in neuroblastoma. Does genetics predict tumour behaviour? Eur J Cancer 31A: 510–515

Bell GI, Yasuda K, Kong H, Law SF, Raynor K and Reisine T (1995) Molecular biology of somatostatin receptors. Ciba Found Symp 190: 65–88

Brodeur GM (1998) Clinical and biological aspects of neuroblastoma. In: The Genetic Basis of Human Cancer, Vogelstein B and Kinzler KW (eds), pp. 691–711. McGraw-Hill: New York

Brodeur GM, Pritchard J, Berthold F, Carlsen NL, Castel V, Castelberry RP, De Bernardi B, Evans AE, Favrot M, Hedborg F, et al (1993) Revisions of the international criteria for neuroblastoma diagnosis, staging, and response to treatment. J Clin Oncol 11: 1466–1477

Caron H, van Sluis P, van Roy N, de Kraker J, Speleman F, Voute PA, Westerveld A, Slater R and Veersteg R (1994) Recurrent 1;17 translocations in human neuroblastoma reveal nonhomologous mitotic recombination during the S/G2 phase as a novel mechanism for loss of heterozygosity. Am J Hum Genet 55: 341–347

Caron H, van Sluis P, van Roy N, de Kraker J, Bobkerink J, Egeler M, Laureys G, Slater R, Westerveld A, Voute PA and Versteeg R (1996) Allelic loss of chromosome 1p as a predictor of unfavourable outcome in patients with neuroblastoma. N Engl J Med 334: 225–230

Dib C, Faure S, Fizames C, Samson D, Drouot N, Vignal A, Millasseau P, Marc S, HAZAN I, Seboun E, Lathrop M, Gyapay G, Morissette J and Weissenbach J (1996) A comprehensive genetic map of the human genome based on 5264 microsatellites. Nature 380: 152–154

Gale G, D’Angio G, Uri A, Chatten J and Koop CE (1982) Cancer in neonates: the experience at the children’s hospital of Philadelphia. Pediatrics 70: 409–413

Kogner P, Borgström P, Bjellérup P, Schilling FH, Reifai E, Jonsson C, Dominici C, Wassberg E, Bihl H, Jacobsson H, Theodorsson E and Hasson M (1997) Somatostatin in neuroblastoma and ganglieneuroma. Eur J Cancer 33: 2084–2089

Lastowska M, Cotterill S, Pearson ADJ, Roberts P, McGuckin A, Lewis I and Bown N (1997a) Gain of chromosome arm 17q predicts unfavourable outcome in neuroblastoma patients. Eur J Cancer 33: 1627–1633

Lastowska M, Roberts P, Pearson ADJ, Lewis I, Wolstenholme J and Bown N (1997b) Promiscuous translocations of chromosome arm 17q in human neuroblastomas. Genes Chromosomes Cancer 19: 143–149

Lastowska M, Van Roy N, Bown N, Speleman F, Lunez J, Strachan T, Pearson ADJ and Jackson MS (1998) Molecular cytogenetic delineation of 17q translocation breakpoints in neuroblastoma cell lines. Genes Chromosomes Cancer 23: 116–122

Look AT, Hayes FA, Shuster JJ, Douglass EC, Castleberry RP, Bowman LC, Smith EI and Brodeur GM (1991) J Clin Oncol 9: 581–591

Martinsons T, Sjöberg RM, Hedborg F and Kogner P (1995) Deletion of 1p loci and microsatellite instability in neuroblastomas analyzed with short-tandem repeat polymorphism. Cancer Res 55: 5681–5686

MartinsonS T, Sjöberg RM, Hallstensson K, Nordling M, Hedborg F and Kogner P (1997) Delimitation of a critical tumor suppressor region at distal 1p in neuroblastomas tumors. Eur J Cancer 33: 1997–2001

Meddeh M, Danglot G, Chudoba J, Vénaut AM, Bénard J, Avet-Loiseau H, Vasseur B, Le Passler D, Terrier-Lacombe MJ, Hartmann O and Bernheim A (1996) Additional copies of a 25 Mb chromosomal region originating from 17q23.1–17qter are present in 90% of high-grade neuroblastomas. Genes Chromosomes Cancer 17: 156–165

Patey YC, Greenwood MT, Kent G, Panetta R and Srikant CB (1993) Multiple gene transcripts of the somatostatin receptor SSTR2: Tissue selective distribution and cAMP regulation. Biochem Biophys Res Commun 192: 288–294

Patey YC, Greenwood MT, Panetta R, Demchyslyshn L, Niznik H and Srikant CB (1995) The somatostatin receptor family. Life Sci 57: 1249–1265

Plantaz D, Mohapatra G, Matthey K, Pellarin M, Seeger RC and Feuerstein BG (1997) Gain of chromosome 17 is the most frequent abnormality detected in neuroblastoma by comparative genomic hybridization. Am J Pathol 150: 81–89

Schilling FH, Ambros PF, Bihl H, Martinsson T, Ambros IM, Borgström P, Jacobsson H, Falkmer UG, Treuner J and Kogner P (1998) Somatostatin receptor expression in vivo is absent in neuroblastomas showing distal deletion of chromosome 1p and di/tetraploid DNA content. Eur J Cancer (in press)

Seeger RC, Brodeur GM, Sather H, Dalton A, Siegel SE, Wong KY and Hammond D (1985) Association of multiple copies of the N-myc oncogene with rapid progression of neuroblastomas. N Engl J Med 313: 1111–1116

Sestini R, Orlando C, Peri A, Tricarico C, Pazzaghi M, Serio M, Pagani A, Bussolati G, Ganchi S and Maggi M (1996) Quantitation of somatostatin receptor type 2 gene expression in neuroblastoma cell lines and primary tumors using competitive reverse transcription-polymerase chain reaction. Clin Cancer Res 2: 1757–1765

Vancompele J, Van Roy N, Van Gele M, Laureys G, Ambros P, Heimann P, Devalk C, Schuuring E, Brock P, Otten J, Gyselinck J, De Paep A and Speleman F (1998) Genetic heterogeneity of neuroblastoma studied by comparative genomic hybridization. Genes Chromosomes Cancer 23: 141–152

Van Roy N, Laureys G, Cheng NG, Willem P, Opdenakker G, Versteeg R and Speleman F (1994) 1;17 translocations and other chromosome 17 rearrangements in human primary tumor neuroblastoma tumors and cell lines. Genes Chromosomes Cancer 10: 103–114

Yamada Y, Post SR, Wang K, Tager HS, Bell GI and Seino S (1992) Cloning and functional characterization of a family of human and mouse somatostatin receptors expressed in brain, gastrointestinal tract, and kidneys. Proc Natl Acad Sci USA 89: 251–255

Zhang CY, Yokogoshi Y, Yoshimoto K, Fujinaka Y, Matsumoto K and Saito S (1995) Association of somatostatin receptor 2 gene in the human small cell lung cancer cell line COR-L103. Biochem Biophys Res Commun 210: 805–815

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