

## ETV6-NTRK3 Gene Fusions and Trisomy 11 Establish a Histogenetic Link between Mesoblastic Nephroma and Congenital Fibrosarcoma<sup>1</sup>

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### Abstract

Congenital mesoblastic nephroma (CMN) is an infantile spindle cell tumor of the kidney that is subdivided into "classical" and "cellular" forms based on the degree of cellularity and mitotic activity. The histogenesis of CMN remains obscure, but relationships to other pediatric renal neoplasms have been proposed. However, cellular CMN is virtually identical histologically to congenital fibrosarcoma (CFS), a malignant tumor of fibroblasts in children of the same age group. Moreover, cytogenetic studies have reported common trisomies in CFS and cellular CMN, particularly of chromosome 11. We show here that t(12;15)(p13;q25)-associated ETV6-NTRK3 gene fusions described in CFS are also present in cellular CMN. ETV6-NTRK3 chimeric transcripts were detected in 8 of 9 cellular CMNs and 2 of 2 mixed CMNs. In contrast, all of the four classical CMNs tested were negative, as were cases of Wilms' tumor and clear cell sarcoma of the kidney. Moreover, we found trisomy 11 only in cellular or mixed CMNs with the ETV6-NTRK3 gene fusion. Our studies indicate that classical and cellular CMN have different genetic features and support the concept that cellular CMN is histogenetically related to CFS. They also provide insight into potential mechanisms involved in the transformation of the classical into the cellular form of CMN.

### Introduction

CMN<sup>3</sup> is a renal spindle cell tumor that occurs predominantly in newborns and very young infants, with most cases being diagnosed before 3 months of age (1, 2). Overall, this tumor represents approximately 5% of renal neoplasms occurring in childhood (3). CMN is subdivided into "classical" and "cellular" forms based on histological features. Classical CMN consists of a moderately cellular proliferation of loosely arranged bland fibroblastic cells, whereas cellular (or atypical) CMN is characterized by high cellularity, numerous mitoses, and cellular pleomorphism (2). Mixed forms are also known to occur, and it has been suggested that cellular CMN may arise from classical CMN. Despite the infiltrative growth patterns seen in all forms of CMN, these tumors are generally thought to have an excellent prognosis with surgery alone being curative (4). However, there are several reports of local recurrences and metastatic spread, and these are almost exclusively associated with the cellular variant (5, 6). It, therefore, remains to be determined whether cellular morphology is predictive of a more aggressive course.

The histogenesis of CMN is unknown. Several lines of evidence

point to a derivation from primitive nephrogenic mesenchyme and a possible relationship to other pediatric kidney tumors (7). A link to WT has been proposed based on similar patterns of loss of heterozygosity involving chromosome 11p13–15 in WT and CMN (8, 9). However, other studies failed to detect loss of heterozygosity of this region in CMN (10). Moreover, the observed pattern in CMN of abundant expression of IGF-II coupled with the lack of WT gene 1 (WT1) expression is distinct from the documented expression of both transcripts in WT (10, 11). In fact, the pattern of expression of these genes in CMN is reminiscent of that observed in CCSK, a highly aggressive pediatric renal neoplasm (12), and it has been proposed that CCSK may be the malignant counterpart of CMN (2).

Cytogenetic analysis of classical and cellular CMN has led to an alternate hypothesis for the derivation of these tumors. The most consistent nonrandom karyotypic finding in CMN is trisomy 11, with additional copies of chromosomes 8, 10, 17, and 20 less commonly reported (13–16). Moreover, trisomy 11 seems to correlate with the cellular phenotype (14–16), whereas classical CMN cases are only rarely associated with this finding (14, 15). This is highly reminiscent of the pattern of trisomy 11 and other trisomies in CFS, a malignant tumor of fibroblasts that occurs in patients aged 2 years or younger and that has striking morphological similarity to cellular CMN (17). CFS is characterized by local recurrence but, like cellular CMN, has an excellent prognosis and a very low metastatic rate (17). Its benign counterpart, IFB, occurs in the same age group as CFS but, like classical CMN, lacks trisomy 11 (18). This, together with ultrastructural similarities, has led to the proposal that classical and cellular CMN are the renal counterparts of IFB and CFS, respectively (19).

We have recently identified a novel t(12;15)(p13;q25) translocation in CFS, and have shown that this rearrangement fuses the ETV6 (TEL) gene from 12p13 with the 15q25 neurotrophin-3 receptor gene, NTRK3 (TRKC; Ref. 20). ETV6-NTRK3 transcripts encoding the HLH protein dimerization domain of ETV6 fused to the protein tyrosine kinase (PTK) domain of NTRK3 were identified in CFS tumors but not in adult-type fibrosarcoma or IFB. The CFS cases studied also showed trisomy 11 (20). Several previous reports have described alterations of chromosomes 12 and/or 15 in CMN (13, 16, 21), including a t(12;15)(p13;q25; Ref. 16). We therefore screened a series of classical and cellular CMN cases for both ETV6-NTRK3 gene fusions and trisomy 11. We found that cellular CMN was strongly correlated with ETV6-NTRK3 expression and trisomy 11, but that classical CMN was negative for both findings. These results suggest that cellular CMN is distinct from classical CMN and is histogenetically related to CFS.

### Materials and Methods

**Clinical Cases.** Primary CMN tumor samples stored at -70°C were collected from the NWTSG tumor bank, British Columbia's Children's Hospital, Children's Hospital Los Angeles, or the CHTN (Columbus Children's Hospital,

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<sup>3</sup> The abbreviations used are: CMN, congenital mesoblastic nephroma; WT, Wilms' tumor; CCSK, clear cell sarcoma of the kidney; CFS, congenital fibrosarcoma; IFB, infantile fibromatosis; RT-PCR, reverse transcriptase PCR; FISH, fluorescence *in situ* hybridization; IGF, insulin-like growth factor; NWTSG, National Wilms' Tumor Study Group; CHTN, Cooperative Human Tissue Network; HLH, helix-loop-helix.

Table 1 Clinical characteristics and molecular genetic findings in CMN cases

CMN subtypes represent pathologic review diagnoses including cellular, mixed, and classical CMN. *ETV6-NTRK3* expression was determined by RT-PCR analysis of RNA isolated from primary tumor tissue, and trisomy 11 was determined by FISH analysis of primary tumor touch preparations using an  $\alpha$ -centromeric chromosome 11 probe.

Case	CMN subtype	Age (months)	Sex	<i>ETV6-NTRK3</i> (RT-PCR)	Trisomy 11 (FISH)
1	Cellular	2	F	+ <sup>a</sup>	+
2	Cellular	16	M	+	+
3	Cellular	1	F	+	+
4	Cellular	2.5	M	+	+
5	Cellular	14 days	M	+	+
6	Cellular	1	F	+	+
7	Cellular	2	F	+	+
8	Cellular	1	M	+	ND
9	Cellular	9	F	-	-
10	Mixed	5 days	M	+	+
11	Mixed	7 days	M	+	+
12	Classical	36	F	-	-
13	Classical	1 day	M	-	-
14	Classical	2 days	M	-	-
15	Classical	2	F	-	-

<sup>a</sup> +, present; -, absent; ND, not determined.

Columbus, OH) during the period 1988 to the present. Cases were diagnosed as classical, mixed, or cellular CMN using established pathological criteria (2).

**RT-PCR Analysis of Tumor Samples.** Total RNA was isolated from primary tumor samples as described previously (22). The presence of viable tumor in tissue blocks was confirmed by frozen section histological analysis. RT-PCR to detect *ETV6-NTRK3* fusion transcripts was performed as previously reported using oligonucleotide primers 541 and TRKC-2 (20). The presence of amplifiable RNA in all of the samples was confirmed by RT-PCR using control primer sets.

**Northern Blot Analysis.** Total RNA (15  $\mu$ g/sample) extracted from frozen primary tumor samples was subjected to Northern blot analysis using established methods. Probes used included full length *ETV6* cDNA (a generous gift of P. Marynen, University of Leuven, Leuven, Belgium), full length *NTRK3* cDNA (a generous gift of B. Nelkin, The Johns Hopkins University, Baltimore, MD), and *TRKC-PTK* (described in Ref. 20).

**FISH Studies.** Touch preparations from frozen primary tumor specimens were made according to conventional methods. An  $\alpha$ -centromeric chromosome 11 probe (Oncor) was used for FISH analysis of the touch preparations according to the manufacturer's instructions. DAPI was used as a chromosome counterstain. Slides were examined using a Zeiss Axioplan epifluorescent microscope equipped with a COHU CCD camera. Images were captured using Perceptive Scientific Instruments, Inc. Powergene software and processed using Adobe Photoshop 3.0.

**Results**

The clinical features of the 15 CMN cases analyzed in this study are summarized in Table 1. These included nine cellular CMNs, two mixed CMNs, and four classical CMNs in eight males and seven females. The diagnosis for each case was based on standard pathological criteria (2) and was confirmed by NWTSG (Edmonton, Alberta, Canada) or CHTN pathological review. All of the cases were in patients 3 years of age or younger, and the majority were in patients younger than 3 months as expected for CMN (2).

Two of the cellular CMN cases from this study (cases 1 and 2 in Table 1) had previous cytogenetic analysis performed on tumor metaphases. Case 1 was previously published as having a t(12;15)(p13;q25) in addition to trisomy 11 and other trisomies (16). Case 2 had a similar karyotype, with a t(12;15)(p13;q24.1), trisomy 11, and other trisomies (data not shown). These findings, coupled with known morphological similarities between cellular CMN and CFS, prompted us to screen the cohort of CMN cases for CFS-associated *ETV6-NTRK3* gene fusions (20). We, therefore, performed RT-PCR to detect *ETV6-NTRK3* fusion transcripts using a previously described assay (20). As shown in Fig. 1, 8 of 9 cellular CMNs and 2 of 2 mixed CMNs were positive for the expected 731-bp *ETV6-NTRK3* fusion transcript, whereas all of the four classical CMNs were negative. Sequencing of the amplification products demonstrated identical fusion sequences as those described for CFS (Ref. 20;

data not shown). We also screened primary tumor tissue from 12 cases of CCSK as well as one case of predominantly spindle cell monomorphic WT in a 16-month-old child. These cases were uniformly negative for identical *ETV6-NTRK3* fusion transcripts (data not shown).

To confirm our results, we performed Northern blot analysis of a cellular and a classical CMN using *ETV6* and *NTRK3* probes. Both samples demonstrated 6.2-, 4.3-, and 2.4-kb *ETV6* transcripts (data not shown), as expected for this ubiquitously expressed gene (23). However, only the cellular CMN expressed a 4.3-kb transcript also hybridizing either a full length *NTRK3* cDNA probe or a probe for the *NTRK3* PTK region (see Fig. 2), as is observed for CFS (20). These data indicate that cellular CMN, but not classical CMN, CCSK, or WT, expresses identical *ETV6-NTRK3* fusion transcripts as those detected in CFS.

We next wanted to determine whether there was a correlation in CMN between the expression of the *ETV6-NTRK3* gene fusion and trisomy 11 as we had previously observed for CFS (20). We therefore prepared touch preparations of each CMN case and probed them with an  $\alpha$ -centromeric chromosome 11 probe. As shown in a representative example in Fig. 3, trisomy for chromosome 11 was observed in every case which expressed *ETV6-NTRK3* fusion transcripts. Trisomy 11 was never observed in CMN cases lacking this gene fusion (see Table 1), including the cellular CMN case that was RT-PCR negative.

**Discussion**

CMN is a renal, spindle cell tumor of infancy that is subdivided into cellular, mixed, and classical forms based on mitotic activity and degree of cellularity. Histological and cytogenetic evidence has suggested that CMN and CFS are histogenetically related. This prompted us to screen CMN cases for the t(12;15)(p13;q25)-associated *ETV6-NTRK3* gene fusion previously reported in CFS. Two of two mixed and 8 of 9 cellular CMNs were positive for the *ETV6-NTRK3* gene fusion whereas all of the four classical CMN cases tested were negative for this alteration. We also found a striking correlation between trisomy 11 and fusion gene expression, with all of the CMN cases harboring the *ETV6-NTRK3* gene fusion

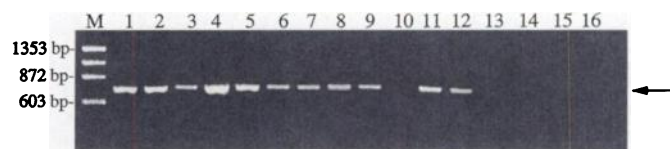


Fig. 1. Detection of *ETV6-NTRK3* fusion transcripts in CMN by RT-PCR. RT-PCR using *ETV6* primer 541 and *NTRK3* primer TRKC-2 demonstrates a 731-bp fragment in a control CFS sample (Lane 1), 8 of 9 cellular CMNs (Lanes 2–10), and 2 of 2 mixed CMNs (Lanes 11 and 12). Four of four classical CMNs were negative (Lanes 13–16).

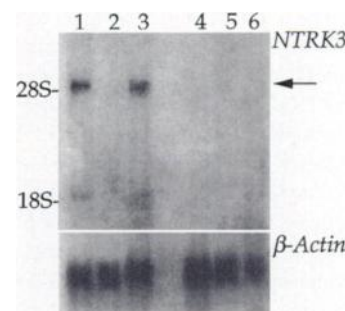


Fig. 2. Northern analysis of CMN cases to detect *ETV6-NTRK3* fusion transcripts. Total RNA isolated from primary tumors and cell lines was subjected to Northern blotting and probed using a 3' *NTRK3* partial cDNA probe encoding the PTK domain (TRKC-PTK; top panel). *NTRK3-PTK* hybridized a 4.3-kb species only in CFS and cellular CMN primary tumor specimens (Lanes 1 and 3, respectively; arrow), whereas classical CMN (Lane 2), the Ewing tumor cell line TC-71 (Lane 4), the neuroblastoma cell line SAN-2 (Lane 5), and human brain RNA (Lane 6) were negative. The bottom panel shows probing of the same blot with  $\beta$ -actin cDNA to test for equal loading.

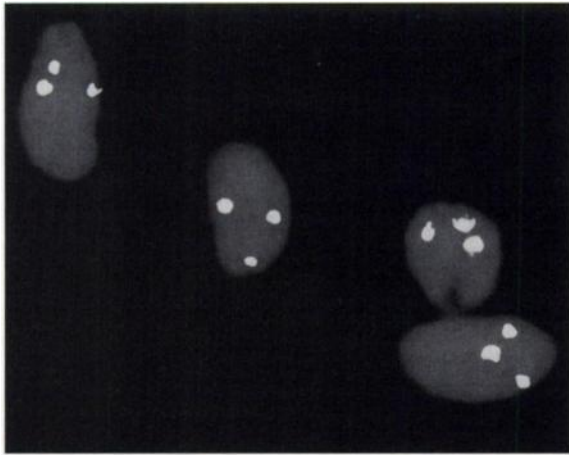


Fig. 3. FISH analysis of trisomy 11 in CMN. Extra copies of chromosome 11 were evaluated by FISH analysis of CMN interphase cells using a chromosome 11  $\alpha$ -centromeric probe. Trisomy 11 was defined by the presence of three chromosome 11 signals (white dots) in at least 25 cells from two separate touch preparations for each sample.

displaying an extra copy of chromosome 11 by FISH. This included two cases (cases 1 and 2, Table 1) with cytogenetically proven extra copies of chromosome 11.

Our findings strongly support the notion that cellular CMN and CFS are histogenetically related. The data do not support a relationship with CCSK or WT as has been previously proposed (see Refs. 2, 8, and 9). Molecular testing for *ETV6-NTRK3* gene fusions, therefore, provides a potential modality for the diagnosis of cellular CMN. Our data also suggest that classical and cellular CMN are genetically distinct entities, inasmuch as no cases with classical morphology displayed either *ETV6-NTRK3* gene fusions or trisomy 11. It is tempting to speculate, as have others (19), that cellular and classical CMN represent the renal counterparts of CFS and IFB, respectively, particularly given the overlapping age ranges of these lesions. The fact that both of the mixed CMN cases tested in this study expressed *ETV6-NTRK3* fusion transcripts lends support to the intriguing possibility that the mixed form represents a transitional stage in which distinct regions within classical CMN have acquired the chromosomal aberrations found in cellular CMN. Tissue microdissection may be useful to address this question.

In a recent survey of 375 CMN cases submitted to the NWTSG, one of the authors (J. B. B.) found that 22% represented classical CMN, 63% were cellular CMNs, and 15% were of mixed phenotype.<sup>4</sup> These data, along with the present study, predict that 75% of CMN cases overall may express *ETV6-NTRK3* gene fusions.

It remains unclear as to how *ETV6-NTRK3* expression confers a proliferative advantage to tumor cells. The gene fusion links the HLH dimerization domain of the *ETV6* *ETS* family transcription factor to the PTK domain of *NTRK3* (20). *NTRK3* is a member of the *NTRK* family of receptor PTKs and binds neurotrophin-3 (NT-3) with high affinity (24). Neurotrophin-3 binding induces receptor dimerization and autophosphorylation of PTK tyrosine residues. These residues serve as anchors for downstream signal transduction molecules such as SHC, phospholipase C $\gamma$  (PLC $\gamma$ ), and phosphoinositid-3 kinase (PI $_3$ -K; Ref. 24). We have hypothesized that the *ETV6-NTRK3* HLH domain induces ligand-independent dimerization and constitutive activation of *NTRK3* signaling (20).

The finding that all fusion-positive CMN and CFS cases demonstrate trisomy 11 suggests that this alteration also contributes to tumorigenesis. The *IGF-II* gene, a paternally expressed member of a cluster of imprinted genes localized to chromosome 11p15.5, encodes an IGF expressed in

certain human tumors and overgrowth syndromes (25). We have recently detected biallelic *IGF-II* expression in a significant proportion of gene fusion-positive CFS and CMN cases but not in negative cases.<sup>5</sup> It is, therefore, possible that some form of complementarity or synergism occurs between *ETV6-NTRK3* and *IGF-II* signaling pathways that is required for CFS or CMN tumor cells to proliferate, as has been observed for other oncogenes (26). Additional studies will be necessary to elucidate the comparative roles of these alterations in oncogenesis and to determine whether this relationship is unique to tumors of very young children.

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<sup>4</sup> J. B. Beckwith, manuscript in preparation.

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