ZFP42: A New Tumor Predisposition Gene? 
Presentation of a Patient with two Neoplasms in Childhood

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Background: The transcription factor ZFP42, located on chromosome 4q35, is a pluripotency marker in early embryonic stem cells. ZFP42 is expressed in embryonic stem cells and downregulated in early development after exposure to retinoic acid. We present a patient who developed a neuroblastoma and a secondary peripheral atypical cartilaginous tumor during childhood. She has a germline rearrangement involving a genomic region close to the ZFP42 gene.

Methods: Data was collected on clinical and tumor characteristics. (Shallow) whole genome sequencing (WGS) was performed on neuroblastoma and whole blood samples. ZFP42 expression of in the cartilage tumor was analyzed using RT-PCR.

Result: WGS revealed a germline rearrangement resulting in the duplication of a 403kbp region and the relocation of a 154kbp region, in between the duplicated regions, on chromosome 4q35. Analysis of publicly available ChIP-seq data of neuroblastoma cell lines revealed the presence of the enhancer marks H3K27ac and H3K4me1 in the 154kbp region that is relocated in the patient. Due to the relocation, this active region is now positioned closer to ZFP42, suggesting "enhancer hijacking". In addition, ZFP42 was detected in the cartilage tumor. Since ZFP42 is involved in the repression of retinoic acid induced differentiation of embryonic stem cells, we hypothesize that the activation of ZFP42 in this patient resulted in a differentiation arrest and subsequent tumor susceptibility.

Conclusion: We present a patient, with a germline rearrangement upstream of ZFP42, who developed two neoplasms in childhood. We propose a role for ZFP42 as a tumor predisposition gene in this patient.

Keywords: Neuroblastoma; Chondrosarcoma; Germline; ZFP42; REX-1
**Introduction**

Neuroblastoma is a developmental malignancy of the neural crest [1]. Tumors typically arise in young children, with a median age of 18 months at diagnosis, and most frequently reside in the adrenal gland or sympathetic side chain [2,3]. The survival rates are high (>85% event free survival) for patients with localized disease, but low (<50%) for patients above 18 months with metastatic disease [2]. Most cases occur sporadically, but familial neuroblastoma is observed in 1-2% of patients [4]. Familial neuroblastoma cases are mostly (80%) attributed to ALK mutations [5,6]. The second most frequently mutated gene in familial neuroblastoma is PHOX2B, causing 6-10% of familial cases [7]. Genetic predisposition to neuroblastoma can also be caused by more general cancer predisposition syndromes, such as neurofibromatosis type 1 (NF1), Li-Fraumeni syndrome (TP53), Costello syndrome (HRAS), Noonan syndrome (PTPN11, KRAS), Beckwith-Wiedemann syndrome (chromosome 11) and Fanconi Anemia (FA pathway) [8].

Chondrosarcoma is a tumor showing cartilaginous differentiation. Chondrocytes, the cartilage producing cells, are partly neural crest derived. It is the second most frequent bone tumor after osteosarcoma, representing about 20% of bone tumors [9]. Tumors arise predominantly between the age of 20 and 60 years. Approximately 85% of chondrosarcomas are classified as conventional chondrosarcomas. These tumors develop in benign enchondromas (central chondrosarcoma) or osteochondromas (peripheral chondrosarcoma) [10]. However, only 1-3% of osteochondromas will develop into secondary peripheral chondrosarcomas [9]. Peripheral chondrosarcoma occurs in younger patients and generally behave less malignant than central chondrosarcomas [11,12]. Prognosis largely depends on histopathological grading based on tumor cell density, mitotic figures and cartilaginous matrix. Atypical cartilaginous tumors/grade I chondrosarcomas, are regarded locally aggressive and rarely metastasize, the 5-yr disease specific survival is estimated at 100% and 10-yr overall survival at 83% [10,12,13]. Grade II and III tumors have higher cell densities and less matrix and 10-yr OS is 64% and 29%, respectively. 10 Predisposition for the development of chondrosarcoma can be caused by germline inactivating mutations in the EXT1 or EXT2 genes, causing hereditary multiple osteochondromas [14-16]. Somatic mosaicism of mutations in IDH1 or IDH2 causes Ollier disease and Maffucci syndrome, which also predispose for development of chondrosarcoma [17,18]. In children, secondary peripheral chondrosarcomas are associated with radiation therapy [19].

ZFP42 is a zinc finger transcription factor, a YY1 transcription factor family member, located on chromosome 4q35, first recognized in 1989 [20,21]. It was identified by its downregulation shortly after treatment with retinoic acid (RA) in F9 teratocarcinoma stem cells, which resulted in differentiation of these cells [20]. ZFP42 was subsequently named REX-1 (for reduced expression).

Although some aspects of the function of ZFP42 are still unclear, ZFP42 is used as a marker of pluripotency for embryonic stem cells and induced pluripotent stem cells. Expression in mouse and human is restricted to embryonic stem cells, tissue specific stem cells and germ cells of the testis [21-23]. A specific role for ZFP42 in cancer is unknown. Being a stem cell marker, it is believed to be expressed in cancer stem cells. Expression has been found in some carcinoma cell lines and in glioblastoma multiforme [20,21]. ZFP42 is positively regulated by Nanog, Sox2, Oct3/4 and Oct6, also known markers for pluripotent stem cells [24,25]. Here, we present a patient with two unrelated neoplasms in childhood, who carries a germline rearrangement, in a genomic region upstream of ZFP42.

**Material and Methods**

**Patient**

The patient’s chart was reviewed for: patient characteristics, symptoms at diagnosis, treatment, pathology reports, radiological and nuclear medicine reports, and urinary excretion levels of homovanillic acid (HVA) and vanillylmandelic acid (VMA).

**Shallow and Whole Genome Sequencing**

Shallow whole genome sequencing was performed on FFPE material of the neuroblastoma as described before [26]. DNA from a whole blood sample was isolated using the DSP DNA Midi kit according to manufacturer’s protocol (Qiagen, Venlo, The Netherlands). Library preparation and sequencing were performed on the HiSeqX sequencing system (Illumina, San Diego, CA, USA), the BCL output was converted using the bcl2fastq tool (Illumina, v.2.20, San Diego, CA, USA) as described before [27]. For analysis and visualization, the “R2: Genomics Analysis and Visualization Platform (http://r2.amc.nl)” was used.

**Cartilage Tumor RNA Isolation**

Twenty µm section of frozen tissue were collected in a tube and dissolved in 5 ml TRIzol. Homogenization was performed using the Ultra-Turrax (IKA, Staufen, Germany). After mixing for 1 min. with chloroform (1 ml), the sample was centrifuged for 30 min. at 15.000xg. A second phenol/chloroform extraction was performed similarly, followed by isopropanol precipitation. The RNA was dissolved in 30 µl MQ. cDNA was synthesized using RevertAid H-Minus FirstStrand cDNA synthesis Kit (Thermo Fisher) according to the recommendations of the manufacturer (372 ng RNA per 20 µl reaction).

**RT-PCR and Gel Electrophoresis**

Reverse transcriptase PCR (RT-PCR) was performed on cDNA using ReadyMix PCR Mastermix (Thermo Fisher), and forward and reverse primers at 500 nM. Forward and reverse primer sequence of ZFP42 were GGCCCTCACAATCTGACTGTC and CTGGGTCTGTGTGGCGTC, respectively. UBC was used as control gene to ensure cDNA quality. Forward and reverse
primer sequence of UBC were ATTTGGTGGCTTCTTG and TGCCCTGACATTCTCGATGGT, respectively. The reaction was performed with heating for 3 min at 95°C, followed by 40 cycles of 30 sec at 95°C, 30 sec at 60°C and 30 sec at 70°C. Subsequently, RT-PCR products were visualized with gel electrophoresis.

**Ethics**

Written informed consent for the use of stored material was obtained from the patient.

**Case Report**

In 1997, a 15-months old girl was diagnosed with neuroblastoma stage 4 in the Democratic Republic of the Congo and the primary tumor in the left adrenal gland was resected. In 2000, the patient immigrated to the Netherlands, still suffering from Iodine-123 Metaiodobenzylguanidine (123I-MIBG) avid metastatic disease (Figures 1A & 1B), histology of a lymph node metastasis showed ganglioneuroblastoma morphology. After 1.5 years of wait-and-see, a 123I-MIBG-avid meningeal metastasis showed progression. Chemotherapy was started, followed by 131I-MIBG therapy, but all metastases were unresponsive. Next, treatment with isotretinoin (13-cis retinoic acid) was administered in an attempt to cause differentiation of the metastases. Chemotherapy resistance in patients with metastatic neuroblastoma is associated with a poor prognosis [28]. However, in this patient, no progression was observed, but a very slow metabolic response was observed by a decrease but not normalization in 123I-MIBG uptake (Figures 1C & 1D) and normalization of HVA 6.25 years after the initial diagnosis. This is an unusual course of disease for a neuroblastoma, as aggressive growth with fatal outcome was expected.

**Figure 1:** Radiological and nuclear imaging of the patient.

Note: Figure 1 (A-D) whole body 123I-MIBG single photon emission computed tomography (SPECT) scans, the arrows indicate pathological 123I-MIBG uptake. A/B) anterior and posterior scans 3 years after diagnosis; C/D) anterior and posterior scans, 6 years after diagnosis. Figure 1 (E-H): conventional X-rays of the left ankle showing: E) an osteochondroma of the distal fibula at the age of 12 years, F/G) anterior/posterior and lateral X-ray at the age of 16 years, showing fast progression of the osteochondroma. H) lateral X-ray of the left ankle after resection of the cartilage tumor. I) T1 weighted MRI at the age of 16 years, showing an osteochondroma of the distal fibula metaphysis with a cartilage cap of 2.6 cm maximum diameter and gadolinium enhancement at the border of the cartilage cap, suspected for secondary peripheral chondrosarcoma development.
At the age of 12 years, the patient developed an osteochondroma, a benign cartilage tumor, at the surface of the left distal fibula (Figure 1E). Over the period of four years this tumor developed into a secondary peripheral chondrosarcoma/atypical cartilaginous tumor as the size of the cartilaginous cap exceeded 2 cm (Figures 1F-1I) [9,29]. Development of a secondary peripheral atypical cartilaginous tumor is exceptional for this age, especially since the patient was not treated with radiotherapy for the neuroblastoma [16,30]. The cartilage tumor was surgically resected (R0 resection) (Figure 1H), no adjuvant chemotherapy was administered. At last follow-up, 20 years after the neuroblastoma diagnosis and 4 years after the secondary peripheral atypical cartilaginous tumor diagnosis, the patient was alive and well. Because the patient developed two different neoplasms during childhood and because her neuroblastoma followed an aberrant indolent clinical course, we tested for germline aberrations.

**WGS of Germline DNA Identifies a Relocation and Duplication Near ZFP42**

![Figure 2: Germline rearrangement.](image)

Note: Figure 2A) Copy number variation (CNV) plot of chr4q35 of the patient in the shallow WGS neuroblastoma sample, showing a duplication in front of ZFP42. 2B) schematic overview of ZFP42 in normal configuration (upper overview) and as found in the germline of the patient (lower overview), blue is the relocated region (A), red the duplicated region (B), green the ZFP42 gene. Chromosomal localization is indicated in kbp resolution. 2C) ChIP-seq results of H3K27ac (red peaks, left) and H3K4me1 (purple peaks, right) in neuroblastoma cell lines (GSE138314 dataset). The blue box indicates the relocated region, the red box the duplicated region.

Whole genome sequencing (WGS) on whole blood of the patient, revealed a germline heterozygous rearrangement on chromosome 4q (Figure 2). In the rearrangement, a 403 kbp region was duplicated and a 154 kbp region was relocated in between the duplicated regions (Figures 2A & 2B). The duplicated region contained no protein coding genes. The relocated region caused breakpoints in the C4orf47, CCDC110, and SORBS2 genes. These genes are not known as tumor suppressor genes. Interestingly, the rearrangement was located near the ZFP42 gene, a pluripotency marker for embryonic stem cells. Due to lack of parental blood
samples, it could not be established if the rearrangement was inherited or de novo. No other germline alterations of relevance were identified. Shallow whole genome sequencing of the neuroblastoma tumor showed a flat copy number variation plot, with the germline duplication on chromosome 4q35 as only structural aberration (Figure 2A). This could either indicate that the tumor content was too low, or that no other chromosomal aberrations were present in the neuroblastoma.

Next, we investigated the epigenetic status of the rearranged regions in a publicly available ChIP-seq dataset (GSE138314) of neuroblastoma cell lines for the enhancer marks H3K27ac and H3K4me1 using the R2 genomics analysis and visualization platform (http://r2.amc.nl). ChIP-seq data of these neuroblastoma cell lines revealed that the 403 kbp region that is duplicated in this patient had near absent levels of H3K27ac and H3K4me1 histone modification marks. However, the 154 kbp region that is relocated in this patient showed higher levels of H3K27ac and H3K4me1 in these cell lines (Figures 2B & 2C). Due to the relocation, a region positive for enhancer marks was positioned near the promoter of ZFP42 in this patient. Therefore, we hypothesized that this could result in activation of ZFP42, which is normally not expressed, by enhancer hijacking.

**ZFP42 is Expressed in Chondrosarcoma of the Patient**

Neuroblastoma tissue was not available for expression analysis of ZFP42. Therefore, we tested ZFP42 expression in the cartilage tumor. From the fresh frozen tumor tissue RNA was isolated and ZFP42 expression was measured using reverse transcriptase polymerase chain reaction (RT-PCR). With RT-PCR, expression of ZFP42 was found in the cartilage tumor (Figure 3). However, expression was low compared to the D341med medulloblastoma cell line, which served as a positive control. Sanger sequencing of the RT-PCR product confirmed the ZFP42 sequence.

**Discussion**

We present a patient who developed two neoplasms in childhood, a disseminated neuroblastoma at 1 year of age with an unexpected indolent course of disease and a secondary peripheral atypical cartilaginous tumor at 16 years of age. We identified a germline rearrangement in chromosome 4q 35, resulting in the positioning of a region positive for enhancer marks near the promoter of the ZFP42 gene, a human stem cell marker [31,32]. ZFP42 was expressed in the cartilage tumor. The combination of two childhood neoplasms, the aberrant course of neuroblastoma disease, and the germline rearrangement affecting a pluripotency marker suggests that the ZFP42 gene is involved in the development of these tumors.

ZFP42 is a stem cell marker which is normally downregulated in early development and which is overexpressed in glioblastoma multiforme and invasive cervical squamous cell carcinoma [31-34]. In glioblastoma downregulation of ZFP42 resulted in a decreased proliferation and increased differentiation.34 However, this result was not confirmed in embryonic stem cells [32,35]. In embryonic stem cells, ZFP42 had a role in inhibiting retinoic acid induced differentiation. Knock-out of ZFP42 resulted in higher degree of differentiation and growth inhibition after treatment with retinoic acid. Overexpression of ZFP42 resulted in less differentiation and an increase in growth [22]. Neuroblastomas are sensitive to retinoic acid, which is used as differentiation treatment in patients [36-38]. Chondrosarcomas undergo growth inhibition after treatment with retinoic acids or selective agonists of RARγ (retinoic acid receptor gamma) in vitro and in vivo [39-42]. However, retinoic acid is not part of the standard chondrosarcoma treatment protocol, as it is in high-risk neuroblastoma treatment [37,39].

Neuroblastoma is a developmental tumor of the neural crest. Tumors arise from a common precursor of the adrenal chromaffin cells and sympathetic neurons. Chondrosarcomas develop from cells committed to cartilaginous differentiation, which are partly neural crest derived and partly mesoderm derived. The precursors of both tumor types are influenced by retinoic acid for differentiation [43]. Based on literature, we propose that ZFP42 inhibits the effect of retinoic acid on differentiation, resulting in a differentiation arrest in the precursor cells. Avoiding differentiation is a crucial step in cancer development [44,45]. However, more research is needed to
confirm the role of ZFP42 in the inhibition of differentiation and the potential role in cancer development.

Conclusion
In conclusion, the patient presented here developed two neoplasms in childhood, a neuroblastoma and a cartilage tumor, of which the precursor cells depend on retinoic acid for differentiation. The patient has a germline mutation affecting ZFP42, a repressor of retinoic acid induced differentiation. We propose a role for ZFP42 as a tumor predisposition gene in this patient.

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Conflict of Interest
All authors declare to have no conflicts of interest

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