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Oligo-astrocytoma in *LZTR1*-related Noonan syndrome

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ABSTRACT

Mutations in *LZTR1*, already known to be causal in familial schwannomatosis type 2, have been recently involved in a small proportion of patients with autosomal dominant and autosomal recessive Noonan syndrome. *LZTR1* is also a driver gene in non syndromal glioblastoma. We report a 26-year-old patient with typical Noonan syndrome, and the dominantly transmitted c.850C > T (p.(Arg284Cys)) variant in *LZTR1*. An oligoastrocytoma was diagnosed in the patient at the age of 22 years; recurrence of the tumor occurred at age 26, as a ganglioblastoma. The patient had been transiently treated with growth hormone between ages 15 and 17. Considering the implication of *LZTR1* in sporadic tumors of the nervous system, we hypothesize that gliomas are a possible complication of *LZTR1*-related Noonan syndrome. This report also supports a possible link between occurrence of a cerebral tumor in Noonan syndrome and a previous treatment with growth hormone.

1. Introduction

LZTR1 (Leucine-zipper-like transcription regulator 1) is a tumor suppressor gene located on 22q11.2, within the 3 Mb region that is most commonly deleted in DiGeorge syndrome, close to *NF2* and *SMARCB1* (which are not located in the common DiGeorge deletion). Although its role in cell physiology remains unclear, *LZTR1* is necessary for regulation of the normal cell cycle. *LZTR1* is a highly conserved gene that contains 6 KELCH- and 2 BTB/POZ functional domains. LZTR1 is an adaptor of the cullin 3-containing E3 ubiquitin ligase complex. It localizes to the Golgi complex. *LZTR1* acts as a tumor suppressor gene: somatic LOF mutations in *LZTR1* occur in 22% of glioblastomas (high-grade astrocytic neoplasms) (Frattini et al., 2013). These authors showed that inactivation of *LZTR1* drives self-renewal and growth of glioma spheres.

Constitutional *LZTR1* loss of function variants causes schwannomatosis type 2 (Piotrowski et al., 2014). Schwannomatosis is an incompletely penetrant dominant disorder clinically defined by the presence of multiple, usually painful spinal, subcutaneous and peripheral nerve schwannomas (including vestibular schwannomas) and rarely meningioma. Schwannomas are nerve sheath tumor composed of Schwann cells, the major neuroglial component of the peripheral nervous system. They are usually benign and slowing growing, although malignant degeneration in neurofibrosarcoma can occur. The molecular signature of schwannomatosis tumors is biallelic inactivation of *NF2* (by mutation and/or 22q deletion) (Ostrow et al., 2017; Plotkin et al., 2013). Whereas *SMARCB1* hypomorphic mutations represents the most common cause of familial schwannomatosis, being mutated in 50% of pedigrees and 10% of the sporadic cases (Hulsebos et al., 2007; Kehrer-Sawatzki et al., 2017), constitutional mutations of *LZTR1* are identified in about 40% of familial and 30% of sporadic patients without mutation in *SMARCB1* (Louvrier et al., 2018; Paganini et al., 2015; Piotrowski et al., 2014). Schwannomatosis-associated *LZTR1* variants are spread in all exons. All reported variants are either protein-truncating or missense predicted to be deleterious (Kehrer-Sawatzki et al., 2017).

Noonan syndrome (NS) is a genetically heterogeneous disorder clinically defined by a variable association of short stature, congenital heart defect and/or cardiomyopathy, a characteristic craniofacial appearance and benign or malignant proliferative disorders, including childhood leukemia and solid tumors of childhood onset. Most genetic

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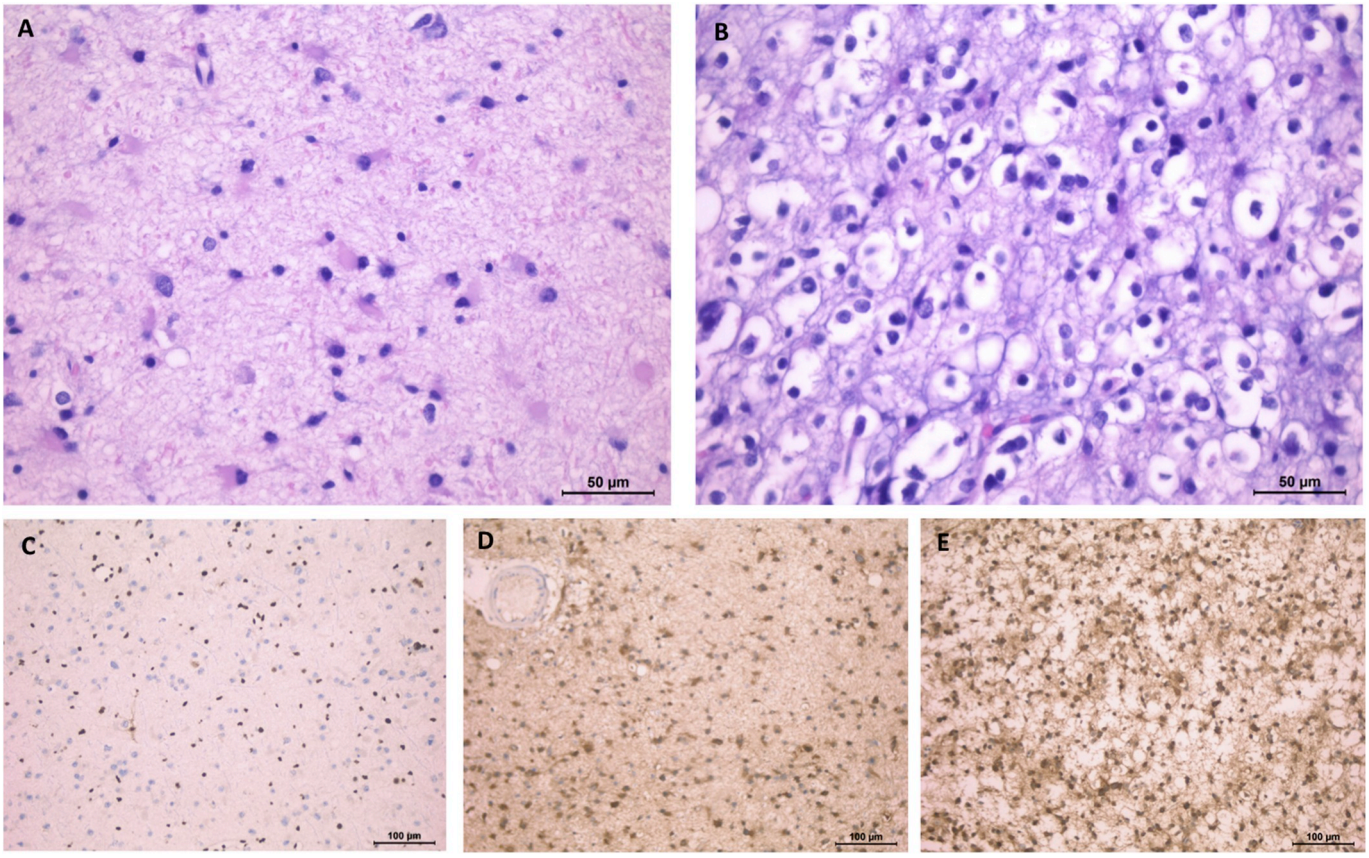

Fig. 1. Histological aspect of the tumor at age 22.
A. H&E staining (400x) showing an astrocytoma component with a gemistocytic pattern. B. H&E staining (400x): oligodendrocyte component (nuclear roundness and perinuclear halo). C. ATRX immunostaining (200x): partial loss of ATRX expression, confirming the presence of a low grade astrocytoma component D. IDH-1 immunostaining (200x): IDH-1 expression in the low grade astrocytoma component E. IDH-1 immunostaining (200x): IDH-1 expression in the oligodendrocyte component.

forms of NS show a demonstrable dysregulation of the RAS/MAPK pathway leading to a sustained or excessive activation of ERK (which defines the RASopathies), with mutations in genes involved upstream in the RAS/MAPK cascade or its regulation. Mutations in *LZTR1* have recently been shown to be another cause of NS (Yamamoto et al., 2015). These authors reported 5 unrelated families with *LZTR1*-related NS and, *a posteriori*, two NS patients screened by WES, but in which the variant was discarded in the original publication (Chen et al., 2014). The patients with *LZTR1*-related NS had the typical NS facial dysmorphism and cardiac abnormalities, short stature, ectodermal involvement, coagulation abnormalities, and cognitive disabilities. Their mutations were all missenses and occurred in the KELCH domains of *LZTR1*. In silico analysis predicted pathogenicity, but functional studies of the variants were not performed. Inheritance of *LZTR1*-linked NS was suggested to be autosomal dominant in the first reports (Chen et al., 2014; Shamseldin et al., 2017; Yamamoto et al., 2015) Recently autosomal recessive inheritance of *LZTR1*-linked NS was demonstrated in twelve families, with mutations ranging throughout the protein, with association of missense, nonsense and splicing variants (Johnston et al., 2018). In recessive pedigrees, some heterozygous parents nevertheless show mild signs of NS, indicating incomplete penetrance of *LZTR1* at heterozygous state (Johnston et al., 2018). So far, variants associated with the dominant form of *LZTR1* are all missense situated in the KELCH domains 3 and 4 of the protein. Different models of pathogenicity are proposed to explain variable transmission modes: dominant negative missense variant in the autosomal dominant form, combination of hypomorphic and loss-of-function variants in the recessive form.

LZTR1 is a new player in the field of NS. Contrary to the other NS genes, the functional link between *LZTR1* and the RAS/MAPK pathway remains elusive, although its involvement in schwannomatosis and its cooperation with LOF in NF2 in the molecular pathogenesis of schwannomas point to a converging action. One adult patient with a dominant form developed “neuromas” on the right hand and forearm, and a lipoma on the thorax. Another family with a recessive form (family 1 in (Johnston et al., 2018)) showed subtle imaging compatible with schwannomas in heterozygous carriers. Interestingly, a NS patient presenting with schwannomatosis has been reported with a mutation in *KRAS* (Bertola et al., 2012). We report here a patient with dominant LZTR1-*linked* NS and an oligoastrocytoma.

2. Clinical report

The patient was born at 37 weeks of gestation with a birth weight of 2300 g (3rd-10th percentile). Early developmental milestones were normal. At the age of 7, he was seen in the genetic department for short stature (height at −2.86 SD), orthopedic troubles (weakness of ankle dorsiflexion and scoliotic attitude) and a maternal family history of Charcot-Marie-Tooth (CMT) syndrome. On clinical exam, he had a normal head circumference (+0.13 SD), impression of downslanting palpebral fissures and hypertelorism, a round face, a wide neck and a shawl scrotum: the clinical features were suggestive for Aarskog or Noonan syndrome but causal genes were not known at that time. The patient and his mother were shown to carry the common 1,7 Mb duplication of *CMT1A*. Evolution of CMT was slowly progressive, with bilateral pes cavus and mild weakness in the four limbs. Cryptorchidism was also present in infancy but resolved spontaneously. He followed normal schooling, but required extra educative support, noteworthy because of his manual dyspraxia and distal muscular weakness. The

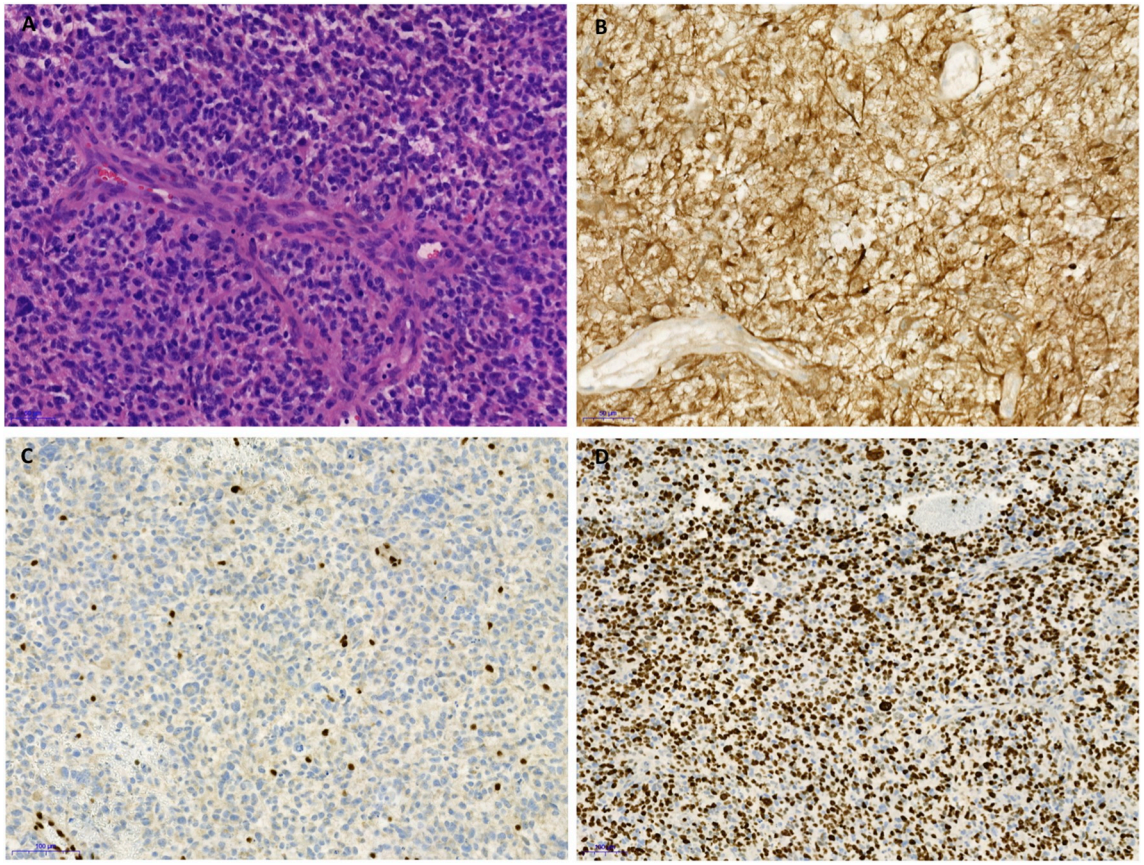

Fig. 2. Histological aspect of the tumor at age 26.
A. H&E staining (200x) showing a highly cellular tumor with features of microvascular proliferation and hyperplastic endothelial cellsB.IDH-1 immunostaining (200x): diffuse nuclear and cytoplasmic IDH-1 expression. C. ATRX immunostaining (150x): diffuse loss of ATRX expression in accordance with the diagnosis of secondary glioblastoma. D.KI-67 immunostaining (100x): high proliferative index (80–90%).

patient was lost to follow up for more than a decade. Short stature was treated with growth hormone between the age of $15^{2/12}$ and $17^{5/12}$ (0.033–0.037 mg/kg/day). At puberty, a rapidly progressive thoracic kyphosis (radius 98°) with scoliosis (radius 37°) and lumbar scoliosis developed that required braces for a couple of years. At the age of 22 years, the patient had several episodes of partial complex seizures. MRI identified a right fronto-temporo-insular tumor encompassing the *arteria cerebri media*. The tumor was surgically removed, followed by radiotherapy. The patient was seen again in genetics at that time. He was 154,5 cm tall (−3,05 SD), weighted 43.3 kg (BMI: 18.4) and had an OFC of 57 cm (+0.16 SD). He had typical NS dysmorphism (triangular face, hypertelorism, ptosis, thick lips with marked philtrum, retrognathia, low set ears and thick helices), a severe kyphoscoliosis with a gibbus, pectus excavatum, and generalized amyotrophy, more marked in the calves. Neurologic examination showed generalized areflexia compatible with CMT. He had no cardiac malformation, no cardiomyopathy, and no hyperkeratosis. Coagulation screen showed a mild defect in factor XI (44%), with normal INR and activated partial thromboplastin time. At the age of 26, the patient presented several new episodes of seizures. Brain MRI detected recurrence of the tumor. The tumor did not respond to chemotherapy with temozolomide followed by PCV (procarbazine, lomustine, vincristine). An attempt to surgically resect the tumor failed and the patient died.

Neuropathological examination of the tumor at the time of the first surgery showed grade II-III oligoastrocytoma with a gemistocytic component (Fig. 1). Most cells showed a heterogeneous GFAP immunostaining, nuclear immunostaining for IDH1, SOX2 and P53, diffuse membrane immunostaining for EGFR. Proliferative index using Ki-67 was 3–4%. By FISH, the lesion showed 19q13 deletion, trisomy 7, but no monosomy 10 and no deletion 1p36. Methylation of MGMT promoter was normal. Neuropathological examination of the relapsing tumor was now grade IV glioblastoma (Fig. 2). ATRX expression was lost in most tumoral cells suggesting an *ATRX* mutation. GFAP immunostaining confirmed the astrocytic component of the tumor as well as the presence of an associated oligodendroglial component. IDH-1 expression was homogeneous. Proliferative index using Ki-67 was 80–90%. Microarray showed no co-deletion 1p/19q and no 22q11 deletion. The p.Arg132His variant in *IDH1* was detected, in keeping with a secondary glioblastoma. The MGMT promoter was methylated.

Genetic screening using a large NGS panel of RASopathy genes identified only a heterozygous variant in *LZTR1*(NM_006767.3): c.850C > T (p.(Arg284Cys)). Analysis of lymphocyte RNA by RT PCR in the proband using standard protocol failed to show aberrantly spliced mRNAs The mutation was inherited from the mother who presented with mild dysmorphic features (ptosis, low-set ears) and kyphoscoliosis, but was not diagnosed as NS in infancy. As an adult, she was 157.5 cm tall (−0.86 SD) and her head circumference was 56.4 cm (+1.23 SD). Except for symptoms related to CMT1A, she did not have any other significant health problems.

3. Discussion

We report a child with NS due to a *LZTR1* variant. His c.850C > T variant falls in the KELCH domain in which are observed the dominant variations of *LZTR1* (Johnston et al., 2018). We confirmed that recessive inheritance was unlikely in this patient: no other variant was identified despite full coverage of the coding sequence, and no splice variant could be detected by RT-PCR. Moreover, no other mutation in

known or suspected NS genes was detected. p.(Arg284Cys) has previously been reported in two instances. This variant was reported as sporadic in a 42-year-old patient with inguinal and spinal schwannomatosis. Her phenotype was not otherwise described, (patient 388 in (Paganini et al., 2015)). It was also observed in a NS family. The segregation of the variant was compatible with dominant inheritance. Affected subjects had no benign or malignant tumor (Yamamoto et al., 2015). Somatic mutation in that amino acid location were also identified in malignant tumor samples (p.Arg284Cys in intestinal adenocarcinoma and endometrioid carcinoma; p.Arg284Ser in an astrocytoma grade IV and p.Arg284His in an intestinal adenocarcinoma) (COSMIC database, http://www.sanger.ac.uk/cosmic).

NS, as other RASopathies, is a cancer-prone disorder (Smpokou et al., 2015). The cumulative risk of cancer in NS is evaluated at 4% at age 20 (Jongmans et al., 2011; Kratz et al., 2011, 2015). *LZTR1* variants have been associated with acute lymphoblastic leukemia in 2 patients (Johnston et al., 2018). Glial tumors of the central nervous system are a well-known complication of RASopathies. The most common form is the low-grade, usually indolent pilocytic astrocytoma of the optic pathway observed in NF1, but there have been multiple reports of NF1 patients with more aggressive CNS lesions: anaplastic medulloblastoma, astrocytoma, oligodendroglioma, high grade glioma (Byrne et al., 2017; Rosenfeld et al., 2010). A recent review identified 22 case reports of NS with brain tumors, mainly dysembryoplasic neuroepithelial tumors (DNET), but also medulloblastomas, oligodendrogliomas, astrocytomas, pilocytic astrocytomas, gliomas and mixed glioneuronal tumors (McWilliams et al., 2016). Two other patients were subsequently reported (Bangalore Krishna et al., 2017). An uncharacterized brain tumor was reported in one *NRAS*-related NS (Altmüller et al., 2017).

In our patient, based on histological findings, cerebral biopsy at diagnosis was compatible with oligo-astrocytoma, a mixed glioma tumor containing both abnormal oligodendroglial and astrocytic cells. The recurrence of the tumor was in the form of a glioblastoma, the most malignant and rapidly growing type of diffuse astrocytoma (WHO grade IV). The presence of IDH-1 mutation (p.Arg132His being the most frequent) differentiates secondary glioblastoma (IDH-1 mutant glioblastoma following the WHO 2016 classification (Louis et al., 2016; Wesseling and Capper, 2018)) from the much more frequent primary glioblastoma (IDH-1 wildtype glioblastoma). In our patient, the molecular signature for the relapsing tumor (IDH-mutant, 1p/19q non-codeleted) with loss of ATRX expression confirms that the secondary glioblastoma originated from the astrocytic component of the precursor tumor (Reuss et al., 2015). No Noonan patient with LOF mutation in *LZTR1* has been reported with glioblastoma, meningioma, or any other malignant CNS tumor so far. Although published evidences seem to split LOF mutations responsible of a peripheral nerve disorder that do not present as a RASopathy from another mechanism of mutations that causes NS, the observation of at least one affected NS patient showing schwannomas may indicate a more complex physiopathology and a role of *LZTR1* mutations in the development of both benign and malignant neuroglial tumors in the central and the peripheral nervous system.

Although GH treatment is generally considered safe in patients with no previous history of cancer (Pekic et al., 2017; Swerdlow et al., 2017), promotion of tumor by GH treatment remains a debated issue in the field of RASopathies. At this point, no clear conclusion can be drawn from the literature, but the increase in tumoral risk has generally been felt to be minimal. In their review on CNS tumors and NS, the authors raised a possible relation with growth hormone treatment (McWilliams et al., 2016). Indication of systematic MRI prior to GH treatment has been discussed (Bangalore Krishna et al., 2017).

Whether *LZTR1*-related NS convey a higher risk of CNS tumors than other NS forms cannot be drawn from a single case report. Nevertheless, involvement of this gene as driver in glioblastoma, and its implication in benign nerve sheet tumors may suggest that tumoral occurrence is not fortuitous.

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