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Letter

A Common Genomic Denominator for Neuroblastoma and Differentiated Thyroid Carcinoma? A Case Series in Children

Madam — We previously hypothesised that children with neuroblastoma harbour a genetically increased risk for the development of differentiated thyroid carcinoma (DTC), irrespective of previous radiation exposure [1]. Here we describe three neuroblastoma survivors who were diagnosed with DTC during follow-up [2] (Table 1). All were treated with ^{131}I-metaiodobenzylguanidine (^{131}I-MIBG) in childhood. Exposure to ^{131}I is a well-known risk factor for DTC development. To prevent thyroidal uptake and potential thyroid damage of ^{131}I during ^{131}I-MIBG treatment, neuroblastoma patients received thyroid protection [2]. As ^{131}I uptake in the thyroid gland on post-therapy scintigraphic images was absent in all three patients, we questioned the causative role of ^{131}I-MIBG therapy in the subsequent incidence of DTC, 6–14 years later (Table 1). Notably, in the landmark Childhood Cancer Survivor Study, the relative risk for thyroid cancer in paediatric neuroblastoma patients compared with leukaemia patients was 2.2 independent of treatment modality [3]. Therefore, we investigated whether a genetic predisposition contributed to the second tumour formation in these patients.

We carried out paired-end whole-genome sequencing on the lymphocyte samples from the three patients and their parents, using Complete Genomics technology. All samples were sequenced to a depth of ~50 and had a coverage of ~97.3% (98.6% for the exome). Detailed methods have been described previously [4].

Only one *de novo* mutation caused an amino-acid change: a p.R1375H substitution in the RasGAP-related domain of NF1 in one patient. As no congenital phenotypical features of neurofibromatosis were seen in this patient, the role of this germline mutation in the onset of neuroblastoma/DTC is uncertain. No structural variants, autosomal-recessive mutations or mutations in other known cancer-predisposition genes were found.

As no DNA changes contributing to the occurrence of DTC in our neuroblastoma patients were detected, we conclude that the subsequent development of DTC was caused by thyroidal exposure to ^{131}I. The relatively long latency time of thyroid cancer development in our patients is in line with this interpretation, as radiation-induced thyroid cancer usually develops after 10–15 years (range 5–30 years) [3].

Table 1
Patient characteristics

	Patient 1 (N457)	Patient 2 (N483)	Patient 3 (N618)
Age at NBL diagnosis (years)	0.75	4.2	0.38
NBL stage (INSS)	III	IV	IV
MYCN gene amplification	No	No	No
^{131}I-MIBG treatments (n)	2	3	4
Total dosage of ^{131}I-MIBG (GBq)	13.0	14.8	11.0
Prescribed thyroid prophylaxis	KI	KI	KI, methimazole, T4
Thyroidal ^{131}I uptake	No	No	No
Chemotherapy courses (n)	2	6	6
High-dose chemotherapy	No	Yes	No
Age at DTC diagnosis (years)	13.3	17.8	6.1
Latency time DTC (years)	12.6	13.5	5.7
Size DTC (cm)	1 × 0.2	3 × 0.1	1 × 1.4
Pathology report	PTC	PTC	PTC
Received treatment for DTC current status	Thyroidectomy +131I complete remission of NBL and DTC	Thyroidectomy complete remission of NBL and DTC	Thyroidectomy +131I complete remission of NBL and DTC

DTC, differentiated thyroid carcinoma; INSS, International Neuroblastoma Staging System; KI, potassium iodide; MIBG, ^{131}I-metaiodobenzylguanidine; NBL, neuroblastoma; T4, thyroxine.

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The absence of visible thyroidal ^{131}I uptake on post-therapy scintigraphic images might indicate that perhaps small amounts of ^{131}I, i.e. not visible on the scans on days 3 and 7 after ^{131}I-MIBG administration, is capable of causing thyroid follicular cell damage and oncogenesis. Alternatively, radiation damage may have occurred due to ^{131}I passing through the vascularised thyroid gland.

Furthermore, the combination of chemotherapy in addition to ^{131}I exposure may also be a trigger in the multi-hit model of DTC development. Indeed, childhood cancer survivors who received chemotherapy in addition to a thyroidal radiation dose <20 Gy were shown to be at 4.0 relative increased risk for the development of DTC when compared with those survivors who did not receive chemotherapy in addition to radiotherapy [5].

In conclusion, our analysis did not reveal a genetic predisposition that underlies the onset of both a neuroblastoma and DTC in children. Exposure to free circulating ^{131}I during ^{131}I-MIBG treatment for neuroblastoma should be considered as the most likely causative factor in the subsequent development of DTC. This conclusion underlines the need for optimal protection of the thyroid during exposure to ^{131}I-MIBG and implies the need for adequate post-treatment surveillance.

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Conflict of interest

The authors declare no conflicts of interest.

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