Cancer spectrum and frequency among children with Noonan, Costello, and cardio-facio-cutaneous syndromes

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Background: Somatic mutations affecting components of the Ras-MAPK pathway are a common feature of cancer, whereas germline Ras pathway mutations cause developmental disorders including Noonan, Costello, and cardio-facio-cutaneous syndromes. These ‘RASopathies’ also represent cancer-prone syndromes, but the quantitative cancer risks remain unknown.

Methods: We investigated the occurrence of childhood cancer including benign and malignant tumours of the central nervous system in a group of 735 individuals with germline mutations in Ras signalling pathway genes by matching their information with the German Childhood Cancer Registry.

Results: We observed 12 cases of cancer in the entire RASopathy cohort vs 1.12 expected (based on German population-based incidence rates). This corresponds to a 10.5-fold increased risk of all childhood cancers combined (standardised incidence ratio (SIR) = 10.5, 95% confidence interval = 5.4–18.3). The specific cancers included juvenile myelomonocytic leukaemia = 4; brain tumour = 3; acute lymphoblastic leukaemia = 2; rhabdomyosarcoma = 2; and neuroblastoma = 1. The childhood cancer SIR in Noonan syndrome patients was 8.1, whereas that for Costello syndrome patients was 42.4.

Conclusions: These data comprise the first quantitative evidence documenting that the germline mutations in Ras signalling pathway genes are associated with increased risks of both childhood leukaemia and solid tumours.

We identified 784 individuals with a mutation-positive RASopathy, of whom 28 were born before 1965 and not in the 0–14 year age range between 1980 and 2012. Hence, their childhood period did not overlap with the activity of the GCCR. Twenty-one additional individuals, who were clearly close relatives, parents or twins of the index person, were also excluded from the analysis. Seven hundred and thirty-five presumably unrelated individuals with a disease-related mutation in one of the Ras pathway genes and whose childhood period overlapped with the activity of the GCCR remained. Testing was performed between 2002 and 2012. The observed distribution of mutated genes in this study population deviates from the true distribution of mutated genes in all RASopathy patients because it is influenced by multiple factors, such as (1) several new genes have been discovered during the observation period 2002–2012 potentially leading to an under-representation of newer genes; (2) patients with mutations in genes giving rise to mild RASopathy phenotypes were less likely to be tested when compared with patients with mutations leading to obvious RASopathy phenotypes. Pathologic germline mutations were detected in PTPN11 (n = 481), SOS1 (n = 81), RAF1 (n = 50), BRAF (n = 41), HRAS (n = 32), Kras (n = 17), SHOC2 (n = 17), MEK1 (n = 8), MEK2 (n = 4), NRAS (n = 3), and CBL (n = 1). As
the clinical syndrome diagnosis was not available for all patients, we used the genetic test results to categorise patients into different syndrome groups (Table 1). Using this strategy, we classified 632 patients with germline mutations of PTEN11, NRAS, SOS1, RAF1, or SHOC2 as having NS. Forty-four of these subjects harboured one of the known recurrent PTEN11 mutations (p.Y279C; p.T468M) that are typically associated with NS with multiple lentigines (LEOPARD syndrome; OMIM 151100), and 17 had a SHOC2 mutation, which causes a clinical variant of NS termed ‘NS-like disorder with loose anagen hair’ (OMIM 607721). Thirty-two patients had CS defined by the presence of a germline KRAS mutation, which causes a clinical variant of NS termed ‘NS-like disorder with loose anagen hair’ (OMIM 607721), and 17 had a SHOC2 mutation, which causes a clinical variant of NS syndrome and CBL syndrome after taking into account the known variability of syndrome groups (Table 1). Using this strategy, we classified 632 patients with germline mutations of CBL as having NS. Forty-four of these subjects harboured one of the known recurrent PTEN11 mutations (p.Y279C; p.T468M) that are typically associated with NS with multiple lentigines (LEOPARD syndrome; OMIM 151100), and 17 had a SHOC2 mutation, which causes a clinical variant of NS syndrome and CBL syndrome after taking into account the known variability of the KRAS mutation-associated phenotypes and the sometimes mild NS-like phenotype associated with CBL mutations (Table 1) (Zenker et al., 2007; Martinelli et al., 2010; Niemeyer et al., 2010).

The 735 individuals included in the final analytic data file contributed 7489.9 person-years of observation. Birth years ranged from 1965 to 2012. Age at genetic testing ranged from 0 to 45 years. The male-to-female ratio was 0.98. Twelve patients with cancer, diagnosed between 2002 and 2012 and diagnosed with a mutation in the years 2003–2012 were identified in this laboratory population (Table 2). To our knowledge, patient 4 is the only patient included in a previous report (Laux et al., 2008).

On the basis of all person-years and the age distribution of the studied population, 1.14 cases of childhood cancer, all sites combined, would be expected vs 12 observed, a 10.5-fold increase (SIR = 10.5, 95% CI = 5.4–18.3) (Table 1). The childhood cancer risk in patients with NS was 8.1-fold increased (95% CI = 3.5–16.0), whereas patients with CS had a 42.4-fold (95% CI = 5.1–153.2) increased risk. A sensitivity analysis, excluding seven cases in whom the cancer and the syndrome diagnosis were made within 1 year of one another demonstrated a cancer risk of SIR 4.4 (SIR = 4.4, 95% CI = 1.4–10.2) for all RASopathies combined. The 17 KRAS syndrome subjects developed two cancers (SIR = 75.8, 95% CI = 9–273.7). There were no cancers observed either among the 53 CFCS patients (495.9 pyo; 0.08 cases expected) or the one patient with CBL syndrome.

SIRs of selected cancers in individuals with NS, CS, and patients with a germline KRAS mutation by cancer type are given in Table 3. High SIRs were observed for JMML in patients with NS (SIR = 717, 95% CI = 148–2094) and in patients with a RASopathy.

### Table 1. Genotype-dependent categorisation of RASopathies identified in 25 genetic laboratories in Germany in 2002–2012

| Syndrome | Mutated gene (n) | n | Observed | Expected | PY | SIR, 95% CI |
|----------|-----------------|---|----------|----------|----|-------------|
| All RASopathies combined | 12 (KRAS) | 12 | 1.14 | 0.00 | 12 | 10.5 (5.4–18.3) |
| NS, all subtypes combined | 632 | 8 | 0.99 | 0.02 | 50 | 8.1 (3.5–16.0) |
| Classic NS | PTPN11 (437), NRAS (3), SOS1 (81), RAF1 (50) | 57 | 7 | 0.89 | 0.02 | 138.9 | 7.9 (3.2–16.2) |
| NSLAH | SHOC2 (17) | 17 | 0 | 0.02 | 0.00 | 0.0 (0.0–159.0) |
| NSML | PTPN11 (44) | 44 | 1 | 0.08 | 0.00 | 496.2 | 13.1 (0.3–72.9) |
| CS | HRAS (32) | 32 | 2 | 0.05 | 0.00 | 278.2 | 42.4 (5.1–153.2) |
| CFCS | BRAF (41), MEK1 (8), MEK2 (4) | 53 | 0 | 0.08 | 0.00 | 495.9 | 0.0 (0.0–45.3) |
| KRAS<sup>b</sup> | KRAS (17) | 17 | 0 | 0.03 | 0.00 | 175.2 | 75.8 (9.2–273.7) |
| CBL<sup>c</sup> | CBL (1) | 1 | 0 | 0 | 0 | – | – |

Abbreviations: NS = Noonan Syndrome; CS = Costello Syndrome; CFCS = cardio-facio-cutaneous syndrome; CI = confidence interval; KRAS = RASopathy with a germline mutation of KRAS; NS = Noonan Syndrome; NSML = NS with multiple lentigines; PY = person-years; SIR = standardised incidence ratio.

<sup>a</sup>Data from the German Childhood Cancer Registry (see Materials and Methods for details).

<sup>b</sup>RASopathy with a germline mutation of KRAS.

<sup>c</sup>RASopathy with a germline mutation of CBL.

### Table 2. Description of 12 individuals with a RASopathy who developed cancer

| Patient (syndrome) | Sex | Age (years) at genetic testing | Amino-acid change (number of cases with this specific mutation in entire cohort) | Neoplasm (age in years) | Mutation previously associated with cancer |
|-------------------|-----|-------------------------------|-----------------------------------------------------------------|------------------------|------------------------------------------|
| PTPN11            |     |                               |                                                                  |                        |                                          |
| 1 (NS)            | F   | 0.2                           | A2G (8)                                                         | JMML (0.1)             | (Strullu et al., 2014)                    |
| 2 (NS)            | M   | 0.4                           | G503R (15)                                                     | JMML (0.2)             | (Strullu et al., 2014)                    |
| 3 (NS)            | M   | 0.4                           | E139D (20)                                                     | JMML (0.3)             | (Strullu et al., 2014)                    |
| 4 (NSML)          | F   | 4                             | Y279C (17)                                                     | ALL (8)                | (Ucar et al, 2006)                       |
| 5 (NS)            | M   | 0.8                           | M504V (25)                                                     | ALL (4)                | (Karow et al, 2007)                      |
| 6 (NS)            | F   | 13                            | G60A (9)                                                       | Pilocytic astrocytoma (7) | (Strullu et al, 2014)                     |
| 7 (NS)            | F   | –                             | N380D (107)                                                   | Dysembryoplastic neuroependothelial tumour (6) | (Strullu et al, 2014)                     |
| 8 (NS)            | F   | 3                             | I282M (1)                                                      | NBL (3)                | (Cosmic database)                        |
| HRAS              |     |                               |                                                                  |                        |                                          |
| 9 (CS)            | M   | 1                             | G12S (24)                                                      | ERMS (1)               | (Kerr et al, 2006)                       |
| 10 (CS)           | F   | 0.5                           | G12C (2)                                                       | ERMS (3)               | (Kerr et al, 2006)                       |
| KRAS              |     |                               |                                                                  |                        |                                          |
| 11 (KRAS)         | M   | 2                             | D153V (4)                                                      | Astrocytoma (2)        | (Schubbett et al, 2006)                   |
| 12 (KRAS)         | F   | 1                             | T581 (1)                                                      | JMML (0.5)             | –                                        |

Abbreviations: ALL = acute lymphoblastic leukaemia; CS = Costello syndrome; ERMS = embryonal rhabdomyosarcoma; F = female; JMML = juvenile myelomonocytic leukaemia; KRAS = RASopathy with a germline mutation of KRAS; NBL = neuroblastoma; M = male; NS = Noonan Syndrome; NSML = NS with multiple lentigines.
of 641 patients with germline RASopathies, as recently documented in an extensive descriptive literature review (Kratz et al, 2011), few epidemiologic studies have investigated this question quantitatively. A recent French study reported the association between JMML and NS in a large cohort of 641 patients with germline PTPN11 mutations. Twenty patients developed JMML and these patients carried specific germline mutation (Selter et al, 2010; Jongmans et al, 2011), suggesting that these tumours are associated with NS. At last, 2 of our 32 patients with a germline HRAS mutation developed ERMS (SIR = 1630, 95% CI = 197–5887), confirming the strong association between CS and ERMS (Gripp, 2005).

Our study has several limitations. (1) We were unable to ascertain cancers in patients older than 14 years, as the case-identifying resource was a childhood cancer registry. Germany does not have an equivalent cancer registry for adults. Thus, the risk of adult-onset cancers in NS, CS, and CFCS cannot be defined completely with the NS-associated JMML literature (Schubbert et al, 2006; Strullu et al, 2014). We detected no novel mutations in our series, confirming earlier conclusions that specific mutations tend to be associated with JMML, that is, that there is a strong correlation between genotype and phenotype in this group of patients. We also confirmed the previously described association between JMML and the rare KRAS p.T58I germline mutation (Schubbert et al, 2006) by identifying another patient with this mutation and JMML among our 17 KRAS subjects, an excess that is statistically significant despite the very small numbers (SIR = 10172; 95% CI = 258–56672) (Table 2).

In agreement with previous case reports, our data suggested an association between PTPN11 germline mutations and ALL (Observed = 2, SIR = 7.1, 95% CI = 0.9–25.6), which did not reach statistical significance. Interestingly, we have previously described another patient from Switzerland with NS and ALL (not included in the current case series) who carried the same PTPN11 M504V germline mutation (Karow et al, 2007) that was also present in one of our two NS/ALL patients (Table 2).

We found three patients with brain tumours in our cohort, consistent with prior reports of somatic mutations in Ras pathway genes in glioma tumour tissue. One patient had a dysmyeloblastic neuroepithelial tumour, a rare central nervous system neoplasm that has previously been described in several other patients with a PTPN11 mutation (Selter et al, 2010; Jongmans et al, 2011), suggesting that these tumours are associated with NS. At last, 2 of our 32 patients with a germline HRAS mutation developed ERMS (SIR = 1630, 95% CI = 197–5887), confirming the strong association between CS and ERMS (Gripp, 2005).

### DISCUSSION

Our study is the first to quantify cancer risk in children with NS, CS, and CFCS. In this population-based study, we observed a significant excess risk for all childhood cancers combined compared with the general population. The elevated overall cancer risk was primarily due to significant site-specific excesses of JMML, ERMS, and brain tumours.

The Ras signalling pathway is frequently activated somatically in a broad spectrum of malignancies (Schubbert et al, 2007). Therefore, it is biologically plausible that individuals with RASopathies who display germline mutations in various Ras pathway genes might be at increased risk of developing cancer. Although a number of case reports and case series have qualitatively suggested an important link between cancer and RASopathies, as recently documented in an extensive descriptive literature review (Kratz et al, 2011), few epidemiologic studies have investigated this question quantitatively. A recent French study addressed the association between JMML and NS in a large cohort of 641 patients with germline PTPN11 mutations. Twenty patients developed JMML and these patients carried specific PTPN11 alleles, suggesting a genotype/phenotype correlation (Strullu et al, 2014). However, these authors included patients that were referred because of the presence of JMML. This approach differed from ours, owing to our efforts aimed at minimising selection bias. Another report from the Netherlands found a 3.5-fold increased risk of all cancers combined in a cohort of 297 individuals with germline PTPN11 mutations (Jongmans et al, 2011). This study that also included adult cancer cases is quantitatively limited by having estimated only risk information for all cancers combined. In addition, this patient series only included patients with a mutation in PTPN11.

We observed three cases of JMML among 519 patients with a germline PTPN11 mutation and one case among 17 patients with a KRAS germline mutation. We observed considerably fewer JMML cases than that observed in the recent French study that reported 20 JMML cases among 641 patients with a PTPN11 mutation (Strullu et al, 2014). However, important methodological differences in study design prevent a direct comparison of these two studies. To reduce the possibility of including individuals with a RASopathy who were diagnosed because of their malignancy, we purposefully excluded one paediatric hematology/oncology laboratory in Germany that focuses specifically on and collects specimens from patients with NS-associated and non-syndromic JMML. This strategy may explain the fact that we found 11 additional cases of NS-associated JMML registered at the GCCR 2002–2012 that were not ascertained in our study population; most of the cases missing from our series were diagnosed by the aforementioned specialised laboratory. Consequently, our JMML-related SIR, while statistically significant, clearly underestimates the actual JMML risk in our population, although it nonetheless provides statistically significant evidence in support of the JMML-RASopathy association.

The mutation spectrum that we identified in the four RASopathy-associated JMML patients (Table 2) overlapped completely with the NS-associated JMML literature (Schubbert et al, 2006; Strullu et al, 2014). We detected no novel mutations in our series, confirming earlier conclusions that specific mutations tend to be associated with JMML, that is, that there is a strong correlation between genotype and phenotype in this group of patients. We also confirmed the previously described association between JMML and the rare KRAS p.T58I germline mutation (Schubbert et al, 2006) by identifying another patient with this mutation and JMML among our 17 KRAS subjects, an excess that is statistically significant despite the very small numbers (SIR = 10172; 95% CI = 258–56672) (Table 2).

The observed excess of JMML risk was primarily due to significant site-specific excesses of JMML, ERMS, and brain tumours. In agreement with previous case reports, our data suggested an association between PTPN11 germline mutations and all cancers (Observed = 2, SIR = 7.1, 95% CI = 0.9–25.6), which did not reach statistical significance. Interestingly, we have previously described another patient from Switzerland with NS and ALL (not included in the current case series) who carried the same PTPN11 M504V germline mutation (Karow et al, 2007) that was also present in one of our two NS/ALL patients (Table 2).

We found three patients with brain tumours in our cohort, consistent with prior reports of somatic mutations in Ras pathway genes in glioma tumour tissue. One patient had a dysmyeloblastic neuroepithelial tumour, a rare central nervous system neoplasm that has previously been described in several other patients with a PTPN11 mutation (Selter et al, 2010; Jongmans et al, 2011), suggesting that these tumours are associated with NS. At last, 2 of our 32 patients with a germline HRAS mutation developed ERMS (SIR = 1630, 95% CI = 197–5887), confirming the strong association between CS and ERMS (Gripp, 2005).
before disease diagnosis. In the case of genetic diseases, it is a reasonable analytic option to begin observation at birth, as affected individuals are truly at risk of disease-related complications before the diagnosis is appreciated. It is likely that, in some instances, the RASopathy diagnosis was prompted by the development of an unusual childhood disease, particularly for JMML, which is widely understood to be an important RASopathy syndrome manifestation. Of note, in seven patients, the cancer and the RASopathy were understood to be an important RASopathy syndrome manifestation. There is no way to evaluate the impact of this subgroup’s absence on our analysis. (5) We excluded the major JMML reference laboratory from this study because it receives samples from children with suspected JMML and did not routinely provide comprehensive RASopathy gene mutation testing, for example, it is likely that the 11 JMML cases identified from the GCCR with a concurrent RASopathy syndrome diagnosis, which did not appear in our cohort, were gene-tested at that institution. Excluding them from our analysis results in a significant underestimate of the JMML risk in this analysis, as noted above. (6) The observed frequency of mutations in the various genes does not represent the true distribution of mutated genes. The observed distribution is influenced by the year of gene discovery.

RASopathies represent monogenic traits, and the underlying rare disease-causing mutations have a high penetrance for the syndrome-defining phenotypic features. However, our data suggest that cancer risks are not markedly elevated in these syndromes. Rather, germline Ras pathway mutations are associated with risks that are significantly greater than those observed in the general population, but which are meaningfully lower than those seen in the more familiar adult-onset cancer susceptibility disorders such as hereditary breast/ovarian cancer and hereditary colorectal cancer. Thus, it appears that germline Ras pathway mutations represent intermediate cancer risk variants, leading to significantly but moderately increased cancer risk. Such rare, intermediate-risk variants are likely to contribute to leukaemogenesis.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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