Genomic instability and genetic heterogeneity in neuroblastoma

AKADEMISK AVHANDLING

Som för avläggande av medicine doktorsexamen vid Sahlgrenska akademin, Göteborgs universitet kommer att offentligen försvaras i hörsal Ivan Östholm, Medicinaregatan 13, Göteborg
Torsdagen den 23 november 2017, klockan 9:00

av

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Avhandlingen baseras på följande delarbeten

I. Schleiermacher G, **Javanmardi N**, Bernard V, Leroy Q, Cappo J, Rio Frio T, Pierron G, Lapouble E, Combaret V, Speleman F, de Wild B, Djos A, Ora I, Hedborg F, Träger C, Holmqvist BM, Abrahamsson J, Peuchmaur M, Michon J, Janoueix-Lerosey I, Kogner P, Delattre O, Martinsson T; Emergence of new ALK mutations at relapse of neuroblastoma. *J Clin Oncol. 2014 Sep 1;32(25):2727-34*

II. **Javanmardi N**, Fransson S, Djos A, Umapathy G, Östensson M, Milosevic J, Kogner P, Hallberg B, Martinsson T, and Palmer RH; The 2p cassette gain in neuroblastoma tumours, A potent combination of ALK, MYCN and the ALK ligand ALKAL2 (FAM150B/AUGa). 2017, *Manuscript*

III. **Javanmardi N**, Fransson S, Djos A, Sjöberg RM, Lorentzen E, Truvé K, Kogner P, Martinsson T; Low frequency ALK hotspots mutations in Neuroblastoma tumours detected by ultra deep sequencing: Implications for ALK inhibitor treatment. 2016, *Manuscript*

IV. **Javanmardi N**, Fransson S, Djos A, Sjöberg RM, Östensson M, Bergerall A, Carén H, Beiske K, Palmer RH, Hallberg B, Noguera R, Kogner P and Martinsson T; Chromosome 11 in high-risk neuroblastoma tumours; A loss and gain pattern indicative of both tumour suppressor and oncogene activity. 2017, *Manuscript*

INSTITUTIONEN FÖR BIOMEDICIN

ISBN: 978-91-629-0336-7 (Print)
ISBN: 978-91-629-0337-4 (PDF)

Genomic instability and genetic heterogeneity in neuroblastoma

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Abstract

Neuroblastoma (NB), a tumour of the sympathetic nervous system and the most common malignant disease of early childhood, is responsible for 9% of paediatric cancer related deaths. Aggressive NB still constitutes a major clinical problem with survival rates of about 35%. It is therefore of great clinical interest to further study the biological parameters that can (i) better classify tumours so that the children may be given the right treatment (ii) identify new actionable targets.

Aim - the objective of this thesis was to explore genes and chromosomal regions with potential involvement in the initiation/progression of NB that can be used for improved patient stratification.

Results – In paper I and III we detected point mutations in the tyrosine kinase domain of the *ALK* oncogene. Minor population of cells with *ALK* mutations were detected with massive parallel deep DNA sequencing. It is likely that early detection of subclones with *ALK* mutation is critical in treatment of these tumours with recently derived small molecule ALK inhibitors. We propose increased serial sampling of tumour material from high-risk NB tumours and analysis with the new sequencing techniques.

In paper II we observed that the distal part of chromosome arm 2p often is subjected to gain of an extra copy – i.e. 2p-gain. Interestingly, this region contains three genes, *ALKAL2*, *MYCN* and *ALK*, of strong importance for NB development. We suggest that the gain of this "cassette" of genes is beneficial to the NB tumor pathogenesis with potential to aid in therapeutical intervention.

In the last study, paper IV, we analysed the high-risk 11q-deleted NB tumours. We show that 11q-deleted tumours with and without *MYCN* amplification present different 11q-deletion breakpoint patterns. The detailed analysis of these patterns enabled us to detect genes and chromosomal regions on 11q that may contain tumour suppressors in this severe child cancer subgroup. Furthermore, we propose *DLG2* as a highly interesting 11q candidate NB gene.

Conclusion - Our observation of a significant spatiotemporal variation of *ALK* mutations is of utmost importance in clinical practice. *DLG2* stands out as a strong tumor suppressor candidate for the 11q-deleted NBs. It is important to note that the experiments we propose are expected to contribute to precision medicine.

Keywords: tumour, neural crest, neuroblastoma, subclone, mutation, relapse, deep sequencing, microarray, 2p, *MYCK, ALK, ALKAL2, 11q, DLG2, CCND1*

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