Göteborg, 2022

Genetic studies of craniosynostosis with focus on syndromic forms

Akademisk avhandling

Som för avläggande av medicine doktorsexamen vid Sahlgrenska akademin, Göteborgs universitet kommer att offentligen försvaras i hörsal Arvid Carlsson, Academicum, Medicinaregatan 3, fredagen den 25 november 2022, klockan 09.00

av Alexandra Ţopa

Fakultetsopponent:

Andrew Wilkie, Professor

Radcliffe Medicinska Avdelningen, Oxfords Universitet, Oxford, Storbritannien

Avhandlingen baseras på följande delarbeten

I. Ţopa A, Samuelsson L, Lovmar L, Stenman G, Kölby L. On the significance of craniosynostosis in a case of Kabuki syndrome with a concomitant *KMT2D* mutation and 3.2 Mbp de novo 10q22.3q23.1 deletion. *Am J Med Genet A. 2017 Aug;173(8):2219-2225.*

II. Ţopa A, Rohlin A, Andersson MK, Fehr A, Lovmar L, Stenman G, Kölby L. NGS targeted screening of 100 Scandinavian patients with coronal synostosis. *Am J Med Genet A. 2020 Feb;182(2):348-356.*

III. Ţopa A, Rohlin A, Andersson MK, Fehr A, Lovmar L, Stenman G, Kölby L. The outcome of targeted NGS screening in patients with syndromic forms of sagittal and pansynostosis - *IL11RA* is an emerging core-gene for pansynostosis. *Eur J Med Genet. 2022 May;65(5):104476.*

IV. Ţopa A, Rohlin A, Fehr A, Lovmar L, Stenman G, Tarnow P, Maltese G, Bhatti-Søfteland M, Kölby L. Genome-wide analysis is an effective diagnostic tool in rare forms of craniosynostosis. *Manuscript.*

SAHLGRENSKA AKADEMIN
INSTITUTIONEN FÖR BIOMEDICIN

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Genetic studies of craniosynostosis with focus on syndromic forms

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Abstract

Craniosynostosis (CS) represents the premature closure of skull sutures and affects ~1 in 2500 children. Untreated CS can lead to significant complications in craniofacial and psychomotor development. The only treatment available is surgical and requires access to highly specialized healthcare. The development of alternative and/or complementary therapeutic methods relies on an understanding of the intricate molecular and cellular mechanisms underlying CS. Genetic studies are of clinical importance to establish an etiologic diagnosis of inheritable craniofacial syndromes and enable patient prognosis and follow-up, including assessment of the recurrence risk in the family (genetic counseling).

The aim of this thesis was to study the prevalence and spectrum of genetic alterations associated with CS in a retrospective cohort of patients that underwent surgery at the largest reference center in Sweden. The patients were initially screened with a targeted next-generation sequencing (NGS) panel covering CS-related genes. Patients with negative outcome were subsequently analyzed using whole-genome or whole-exome sequencing (WGS and WES, respectively).

The results showed that targeted NGS screening demonstrated a high diagnostic yield in patients with syndromic forms of CS (>80%) regardless of sutural pattern. The particular case of a patient with coronal synostosis and a Kabuki-like phenotype, as well as a simultaneous de novo occurrence of a lysine-specific methyltransferase 2D (*KMT2D*) mutation and 10q22.3q23.1 microdeletion, suggests that CS may be an underdiagnosed feature of these conditions. Additionally, interleukin-11 receptor subunit α (*IL11RA*) was highlighted as an emerging core gene for autosomal recessive pansynostosis. The use of WGS/WES detected causal variants in 38% of the patients with rare syndromic forms of CS and a negative outcome at targeted screening. Furthermore, potentially relevant variants were observed in 87% of the remaining patients with syndromic or nonsyndromic forms of CS.

These findings showed that both targeted NGS screening and WGS/WES demonstrated a high diagnostic yield in patients with syndromic CS. Moreover, the results suggested that WES/WGS has the potential to become a unique diagnostic tool that can be adapted to the phenotypic presentation by initial use of in silico gene panels, followed by exome/genome-wide analysis of rare forms of CS.

Keywords: cranial, suture, genetic, diagnostic, next generation sequencing

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