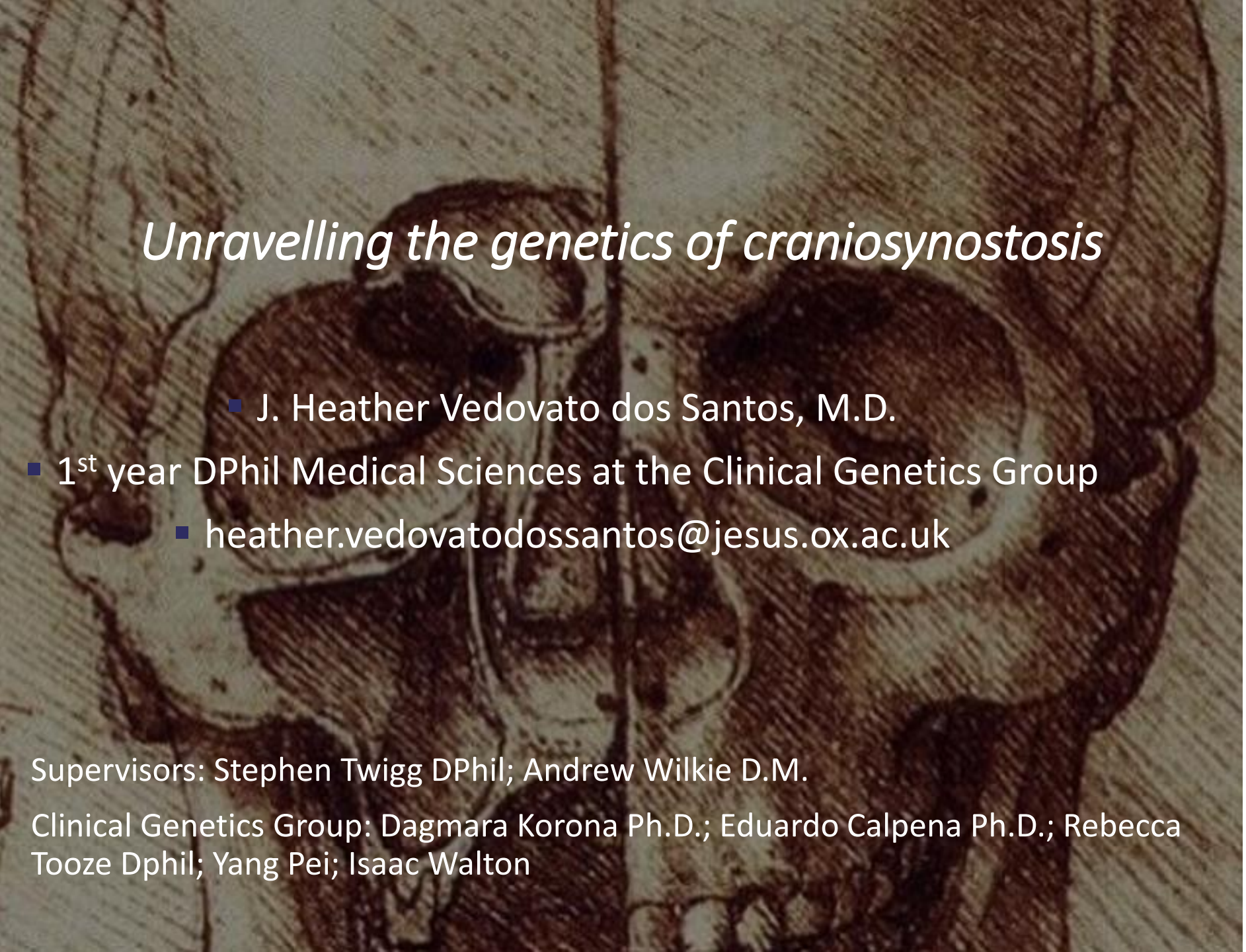

Unravelling the genetics of craniosynostosis

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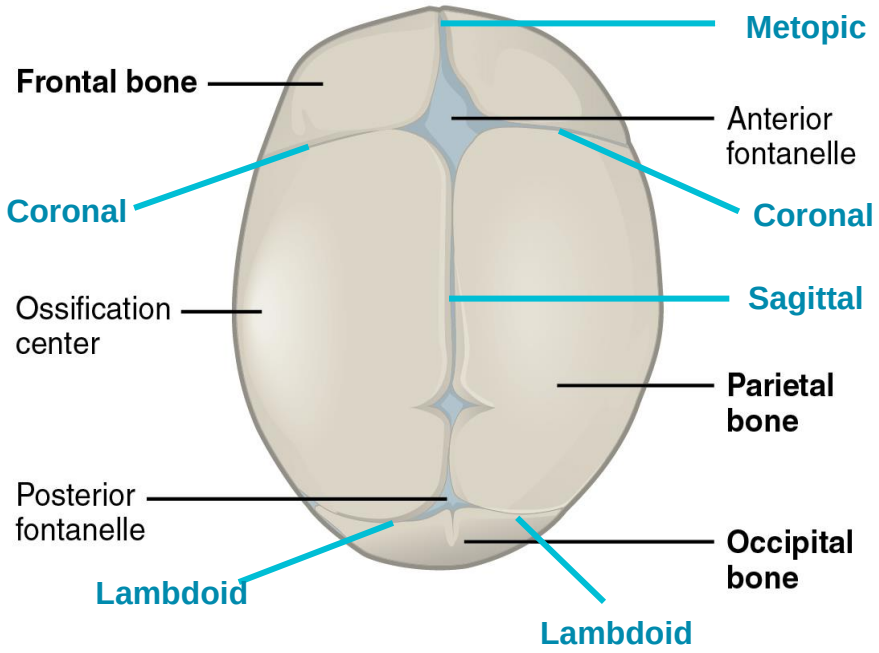
The VTCT Foundation

Craniosynostosis



Why does a genetic diagnosis matter?

Medical

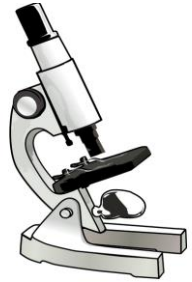
- There may be specific complications to screen for
- Management implications
- Treatment

Families:

- Ends the diagnostic odyssey
- Having a name opens doors for extra support
- Better counselling: recurrence risks
- Testing of wider family
- Preimplantation or prenatal genetic testing

Research:

- New information about skull and suture development
- Essential for future prevention and treatment strategies

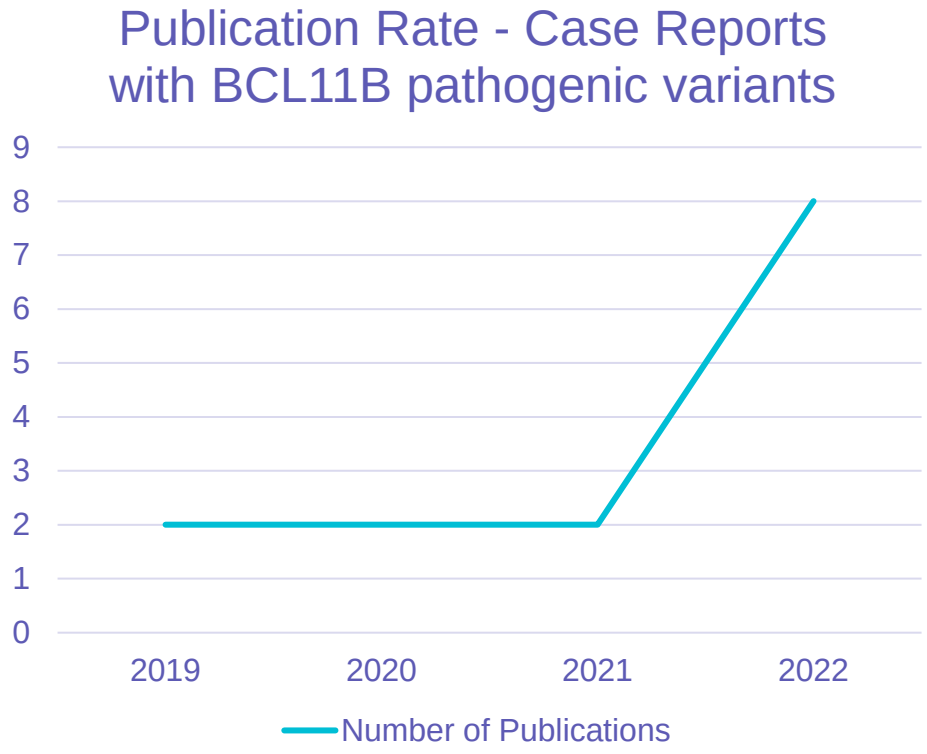


BCL11B-related disease

BCL11B-related disease

BCL11B-related disease

2016 → 2018 → 2019 → 2023



- There is an increasing number of patient reports
- Our group was aware of several other patients with craniosynostosis and variants in BCL11B
- We decided to:
  1. Review the literature
  2. Gather and analyze information about patients with craniosynostosis and *BCL11B* variants

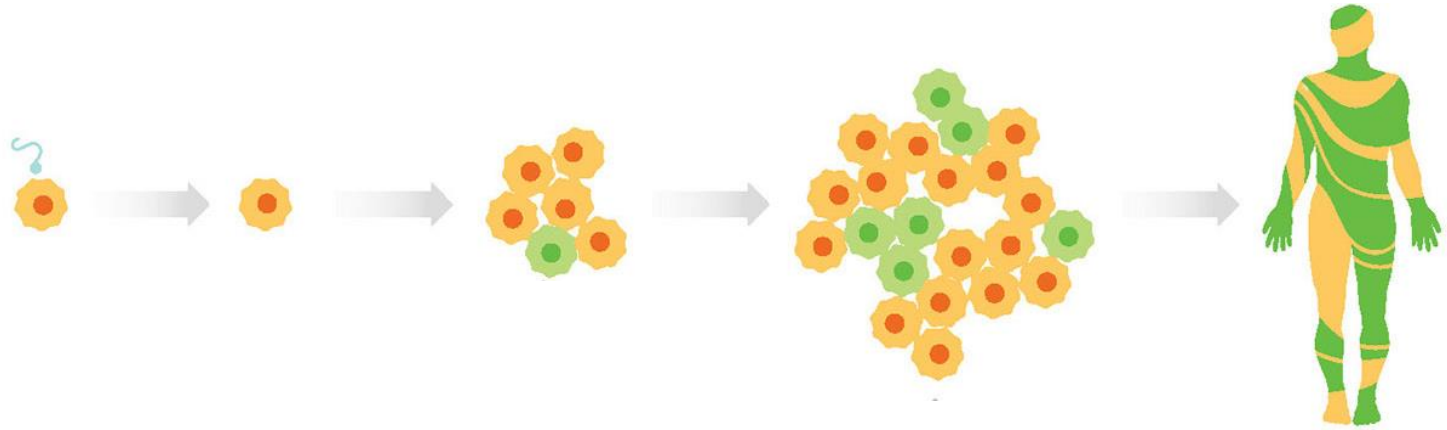
Literature Review and Case reports

- November, 2022 to March, 2023
- MEDLINE and Embase (444/656 results)
- Search word: “BCL11B”
- Inclusion criterium: mention of a patient with a germline pathogenic/likely pathogenic variant in *BCL11B*
- Snowballing + alert system

31 patients in 18 papers

Patient	Age	CRS	Other features
Patient 1	9y	Yes	Yes
Patient 2	3y	Yes	Yes
Patient 3	14y	Yes	Yes
Patient 4	3y	Yes	Yes

Patient 1



- Female, 9 years 5 months old
- Craniosynostosis (left unicoronal)
  – 1 surgery at 1y8m
- Variant in mosaic state

Patient 2

- Male, 3 years and 4 months
- Craniosynostosis (coronal bilateral, right temporoparietosquamosal) – 1 surgery

Patient 4

- Female, 3 years 11 months of age
- Unicoronal craniosynostosis
- Facial dysmorphism
- Early developmental impairment
- Food allergies and sleep disturbances

1. BCL11B is a neurodevelopmental phenotype characterized by a triad of cardinal features

Cardinal features (present in ≥ 80%)	Freq
Neurodevelopmental disorder	**97%**
• Intellectual deficiency / Learning difficulties	97%
• Delayed motor milestones	97%
• Speech Impairment	87.5%
Dysmorphic features	**97%**
Immune deficiency	**83%**
• Frequent/atypical infections	38%
• Laboratory anomalies	88%

Major features (present in ≥ 25%)	Freq
Dental anomalies	54%
Allergies/Asthma	52%
Feeding difficulties	45%
Brain MRI anomalies	38%
Refractive error	33.33%
Autistic features	26%

2. BCL11B-related disease has a subtle but recognizable facial phenotype

Facial Features	Freq
Long Philtrum	90%
Thin upper lip vermillion	89%
Thin/Sparse eyebrows	86%
Nose dysmorphism	79%
Thin eyebrows	74%
Hypertelorism	70%
Small Palpebral Fissures	46%

3. Craniosynostosis is a major feature of BCL11B-related disease

Cardinal features (present in ≥ 80%)	Freq
Neurodevelopmental disorder	**97%**
• Intellectual deficiency / Learning difficulties	97%
• Delayed motor milestones	97%
• Speech Impairment	87.5%
Dysmorphic features	**97%**
Immune deficiency	**83%**
• Frequent/atypical infections	38%
• Laboratory anomalies	88%

Major features (present in ≥ 25%)	Freq
Dental anomalies	54%
Allergies/Asthma	52%
Feeding difficulties	45%
Brain MRI anomalies	38%
Refractive error	33.33%
Craniosynostosis	**28%**
Autistic features	26%

Major take-aways

- First report of a patient with somatic mosaicism for the pathogenic variant
- First report of a patient with a whole-gene deletion leading to this phenotype
- Delineation of the clinical characteristics of BCL11B—related disease – addition of craniosynostosis to the list of major features
- Documentation of the evolution of the facial phenotype over time

Major take-aways

- BCL11B-related disease is a neurodevelopmental phenotype with 3 cardinal features
- From the dysmorphological standpoint there is a characteristic facial phenotype – this is similar to that of fetal alcohol syndrome
- Craniosynostosis is a major feature. Undiagnosed patients with craniosynostosis should be tested for BCL11B variants
- If sequencing is negative, patients should be investigated for deletions involving BCL11B

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