TRPM3-related craniosynostosis presenting with arrhinia, cleft palate and other developmental anomalies: two very rare case reports

Lord Jephthah Joojo Gowans[1,2], Solomon Obiri-Yeboah[2], Gideon Okyere Mensah[1], Mavis Dansowaa Asante[1], Daniel Kwesi Sabbah[2], Alexander Acheampong Oti[2], Gyikua Plange-Rhule[3], Tamara Busch[4], Azeez Butali[4], Michael Lawrence Cunningham[5,6], Peter Donkor[7]

[1]Department of Biochemistry and Biotechnology, Kwame Nkrumah University of Science and Technology (KNUST), Kumasi, Ghana, [2]School of Dentistry, KNUST, Kumasi, Ghana, [3]Department of Child Health, School of Medical Sciences, KNUST, Kumasi, Ghana, [4]Department of Oral Pathology, Radiology and Medicine, College of Dentistry, University of Iowa, Iowa City, USA , [5]Department of Pediatrics, Division of Craniofacial Medicine, University of Washington, Seattle, WA, USA, [6]Center for Developmental Biology and Regenerative Medicine, Seattle Children's Research Institute, Seattle, WA, USA., [7]Department of Surgery, School of Medical Sciences, Kwame Nkrumah University of Science and Technology, Kumasi, Ghana.

Correspondence: Ljj.gowans@gmail.com/Ljjgowans@knust.edu.gh

INTRODUCTION

- Premature differentiation of cranial suture mesenchyme to osteoblasts culminates in craniosynostosis (CS)[1]
- Ultimately, cranium morphology is altered, potentially retarding brain development and function[2]
- ~30 of CS cases present with additional dysmorphologies, such as proptosis, syndactyly and ptosis[3]
- There are >180 genetic syndromes that may exhibit CS[4]
- Mutations in several genes can lead to these syndromes; e.g., *EFNB1, FGFR1, FGFR2, FGFR3, TWIST1, ERF* and *TCF12*[5]
- Though FGFR-related syndromes like Apert and Crouzon are the predominant ones, several rare syndromes can present with CS[5]

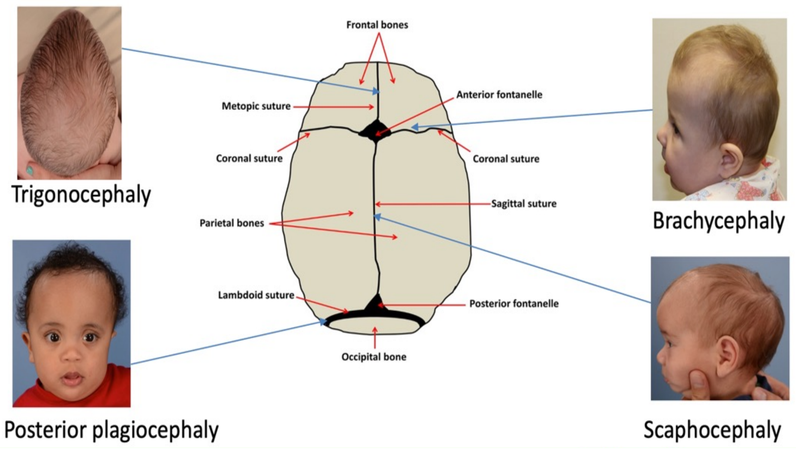

Figure 1. Clinical presentation of craniosynostosis[1].

AIMS OF THE STUDY

- Ascertain genetic risk factors for two patients presenting with CS and several developmental anomalies.
- Identify possible genetic modifiers responsible for variable expressivity of phenotypes in individuals carrying mutations in the same gene.

SUBJECTS AND METHODS

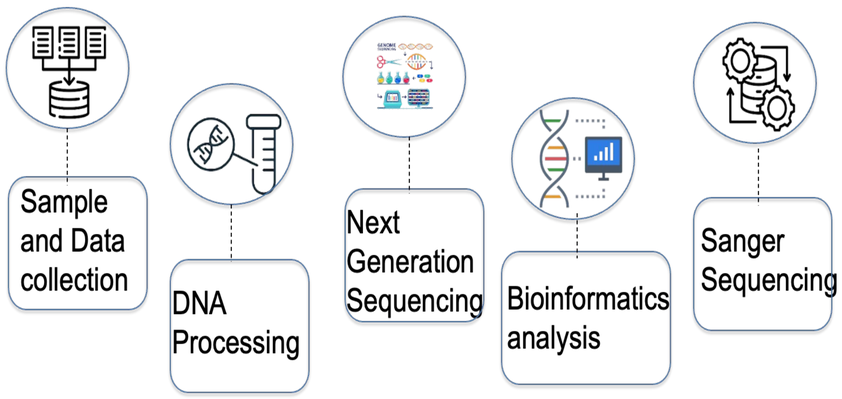

Figure 2. Outline of entire workflow

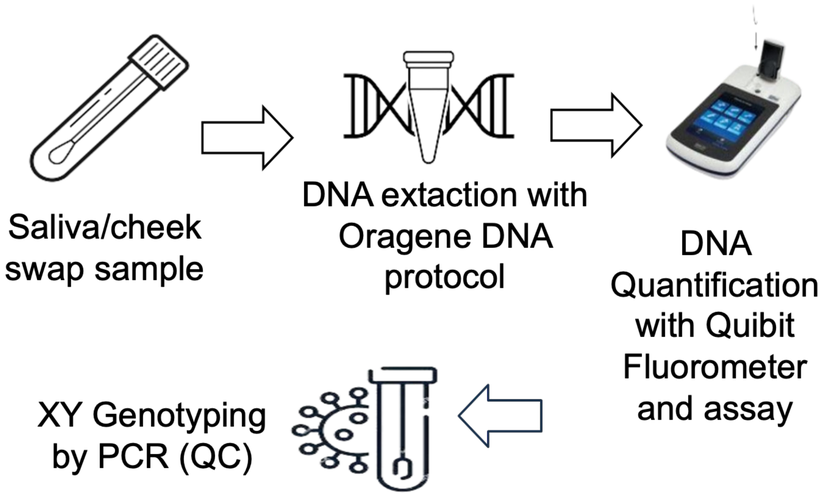

Figure 3. Overview of DNA processing

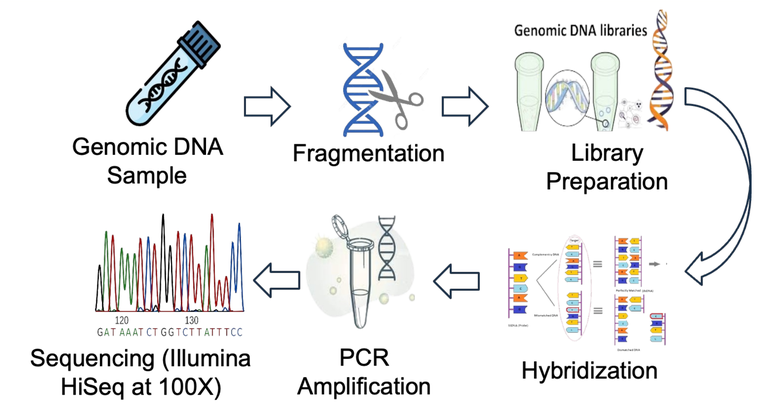

Figure 4: Whole exome sequencing workflow

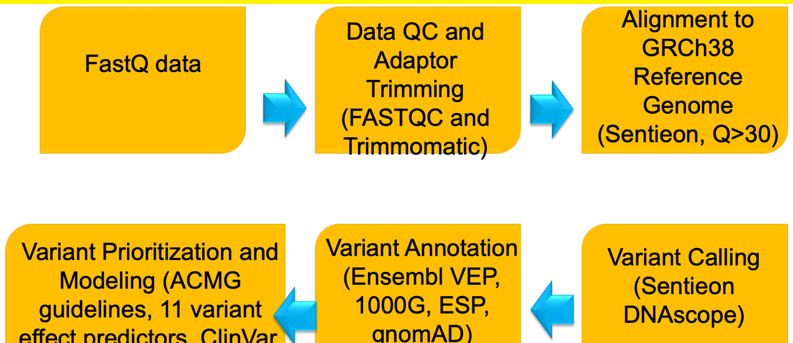

Figure 5: Bioinformatics analyses workflow

RESULTS AND DISCUSSION

Table 1. Clinical phenotypes observed in probands.

Participant ID	Observed phenotypes
GH20209008_1	Evaluation at age 1 year: Female. Craniosynostosis involving all sutures. Arrhinia (nose absent) - eats and breath through mouth. Microcephaly. Developmental delay - not walking at 1 year. V-shaped eyebrow that meet at midline. Erupting teeth (central incisors). Evaluation at age 5: Synophrys. She started walking at 5 years old.
GH20239021_1	Male and recruited at 1.5 years. Sagittal craniosynostosis. Incomplete cleft palate. Low-set ears.

Figure 6: Clinical presentation of proband GH20209008_1.

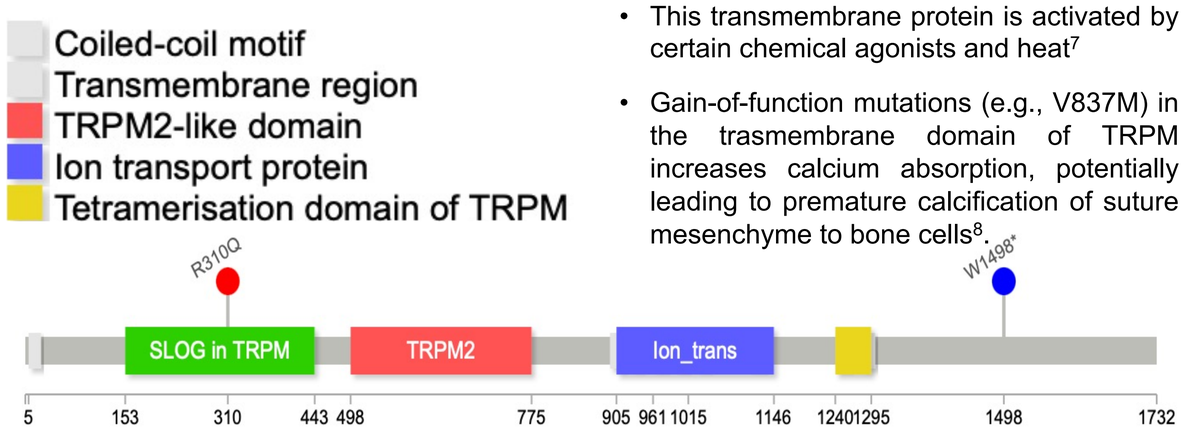

Figure 7: Distribution of the observed variants in various domains of the TRPM3 protein.

Table 2. Pathogenic variants of craniofacial importance observed in the two families.

Family ID	Genomic coordinate	Gene	Transcript ID	HGVSc	HGVSp	NTP
GH20209008	**Chr9:70536620 (Novel)**	***TRPM3***	**ENST00000677713**	**c.4493G>A**	**p.Trp1498Ter**	**1***
	Chr15:56094927 (rs376549300)	*RFX7*	ENST00000559447	c.2801T>G	p.Phe934Cys	6
	Chr2:235042606 (rs142429272)	*SH3BP4*	ENST00000392011	c.1837C>G	p.Pro613Ala	6
	Chr1:180274553 (rs770324044)	*LHX4*	ENST00000263726	c.1147G>C	p.Asp383His	9
	Chr11:31793530 (Novel)	*PAX6*	ENST00000643871	c.940A>G	p.Met314Val	6
	Chr20:64232334 (rs1318392943)	*MYT1*	ENST00000328439	c.2846C>T	p.Pro949Leu	11
	Chr8:28717689 (Novel)	*EXTL3*	ENST00000220562	c.1630C>A	p.Pro544Thr	6
	Chr1:21885337 (rs1553171928)	*HSPG2*	ENST00000374695	c.1193G>A	p.Ser398Asn	11
	Chr16:53664963 (Novel)	*RPGRIP1L*	ENST00000647211	c.1150C>T	p.Gln384Ter	1#
	Chr1:150557329 (rs371872840)	*ADAMTSL4*	ENST00000271643	c.2041G>A	p.Gly681Arg	10
	Chr3:47412742 (rs111678754)	*PTPN23*	ENST00000265562	c.4468G>A	p.Gly1490Ser	7
	Chr1:5874499 (rs764323785)	*NPHP4*	ENST00000378156	c.3203T>G	p.Phe1068Cys	7
	Chr2:107860796 (rs777730182)	*RGPD4*	ENST00000408999	c.1789C>T	p.Arg597Ter	1&
GH20239021	**Chr9:70827891 (rs764482582)**	***TRPM3***	**ENST00000677713**	**c.929G>A**	**p.Arg310Gln**	**10**
	Chr2:121447504 (Novel)	*CLASP1*	ENST00000263710	c.1745C>T	p.Ser582Phe	6
	Chr6:133481504 (COSV62046197)	*EYA4*	ENST00000355286	c.1012G>T	p.Asp338Tyr	6

All variants were observed in a heterozygous state. *CADD score = 43, #CADD score = 42, &CADD score = 40

- Pathogenic variants in *TRPM3* (e.g., V837M) cause Neurodevelopmental disorder with hypotonia, dysmorphic facies, and skeletal anomalies, with or without seizures (NEDFSS) - OMIM# 620224[7]
- TRPM3 is a non-selective cation channel with high permeability for calcium ions (Ca^{2+}), an essential element for bone formation[7]
- This transmembrane protein is activated by certain chemical agonists and heat[7]
- Gain-of-function mutations (e.g., V837M) in the trasmembrane domain of TRPM increases calcium absorption, potentially leading to premature calcification of suture mesenchyme to bone cells[8].

CONCLUSION AND RECOMMENDATIONS

- Our study confirms the contribution of *TRPM3* pathogenic mutations to the aetiology of syndromic craniosynostosis.
- Pathogenic variants in *TRPM3* exhibit variable expressivity, including skeletal anomalies like CS and dysmorphic facies.
- Pathogenic variants in other genes (*RFX7, SH3BP4, LHX4, PAX6* and *MYT1*) may underly co-occurring autosomal dominant syndromes that may present with additional phenotypes.
- All other genes may not contribute to the phenotypes since they are associated with autosomal recessive conditions but were observed in the heterozygous state in the current study.
- Whole exome sequencing should be adopted when syndrome diagnosis is uncertain based on clinical presentations.
- Our findings is crucial for CS pathophysiology, diagnosis, genetic counselling and personalized medicine.

Funding: R21TW011729, Fogarty International Center (FIC)/National Institutes of Health (NIH), USA

REFERENCES

1. Kajdic N, Spazzapan P, Velnar T. (2018). Craniosynostosis - Recognition, clinical characteristics, and treatment. Bosn J Basic Med Sci.;18(2):110-116.
2. Stanton E, Urata M, Chen JF, Chai Y. (2022). The clinical manifestations, molecular mechanisms and treatment of craniosynostosis. Dis Model Mech.;15(4):dmm049390.
3. Katouni K, Nikolaou A, Mariolis T, Protogerou V, Chrysikos D, Theofilopoulou S, Filippou D. (2023). Syndromic Craniosynostosis: A Comprehensive Review. Cureus.;15(12):e50448.
4 Greenwood J, Flodman P, Osann K, al. (2014). Familial incidence and associated symptoms in a population of individuals with nonsyndromic craniosynostosis. Genet Med.;16(4):302-10.
5 Wilkie AOM, Johnson D, Wall SA. (2017). Clinical genetics of craniosynostosis. Curr Opin Pediatr.;29(6):622-628.
6. Wei X, Huang G, Gui B, Xie B, Chen S, Fan X, Chen Y. (2022). Phenotypic variability of syndromic craniosynostosis caused by c.833G > T in FGFR2: Clinical and genetic evaluation of eight patients from a five-generation family. *Mol Genet Genomic Med.*;10:e1901.
7. Lines MA, Goldenberg P, Wong A, Srivastava S, Bayat A, Hove H, Karstensen HG, et al. (2022). Phenotypic spectrum of the recurrent TRPM3 p.(Val837Met) substitution in seven individuals with global developmental delay and hypotonia. Am J Med Genet A.;188(6):1667-1675.
8. Gauthier LW, Chatron N, Cabet S, et al. (2021). Description of a novel patient with the TRPM3 recurrent p.Val837Met variant. Eur J Med Genet. 2021 Nov;64(11):104320.