

Craniosynostosis

Andrew O M Wilkie

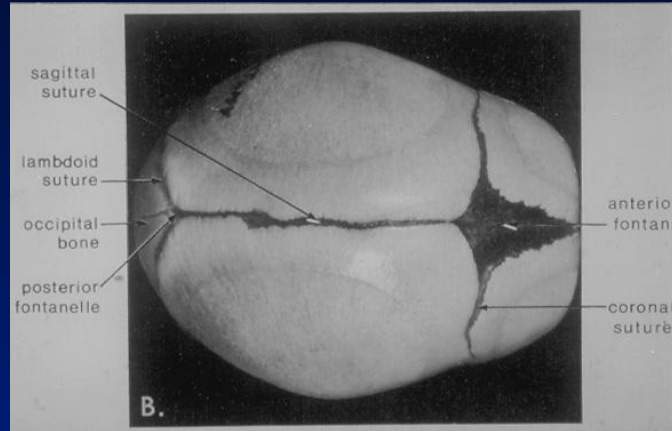
**MRC Weatherall Institute of Molecular Medicine,
University of Oxford**

**Craniofacial Unit,
Oxford University Hospitals NHS Trust**



Craniosynostosis: premature fusion of the cranial sutures

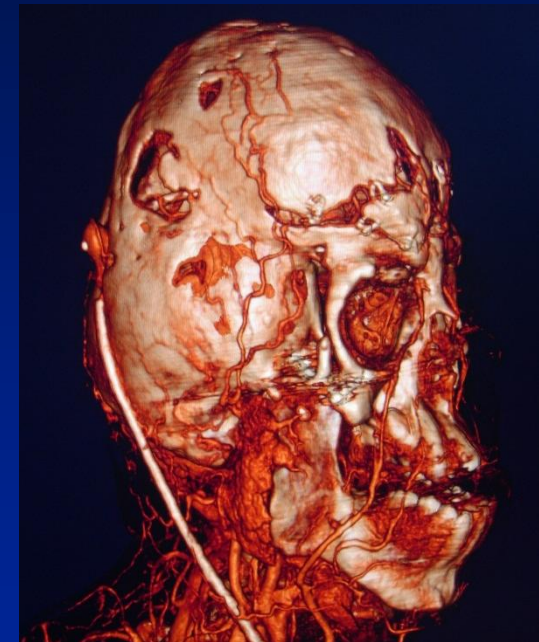
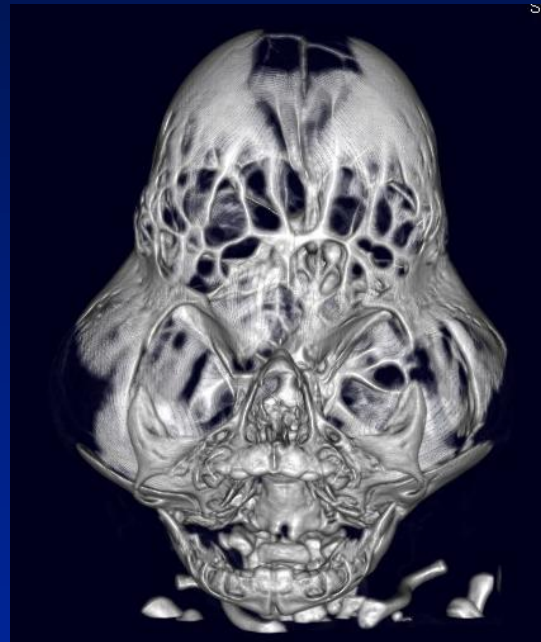
Prevalence ~1 in 2,000



normal sutures



L coronal synostosis



Management of craniosynostosis tends to be organised at a national scale

england.nhs.uk/commissioning/spec-services/npc-crg/group-e/specialised-surgery-in-children/

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Specialised surgery in children

Scope

This Lead and Inform Clinical Reference Group (CRG) covers a large number of specialities and diagnoses. This is because specialised surgery in children comprises both the ongoing management of congenital abnormalities and serious acquired conditions during childhood. The services included but not limited to:

- specialist ear, nose and throat services for children (including specialist audiology services)
- specialist gynaecology services for children
- specialist orthopaedic surgery services for children
- specialist plastic surgery services for children
- specialist paediatric surgery services
- specialist paediatric urology services
- specialist dentistry services for children
- cleft lip and palate services
- **craniofacial services**
- surgery for complex obesity in children
- paediatric chronic pain services
- surgery for neonates



Clinical Teams

Craniofacial Unit, Oxford



Core team includes:

Plastic, Maxillofacial, Neuro-surgeons
Anaesthetists
Ophthalmologists, Orthoptists
Psychologists
Speech & Language Therapists

Craniofacial Geneticists

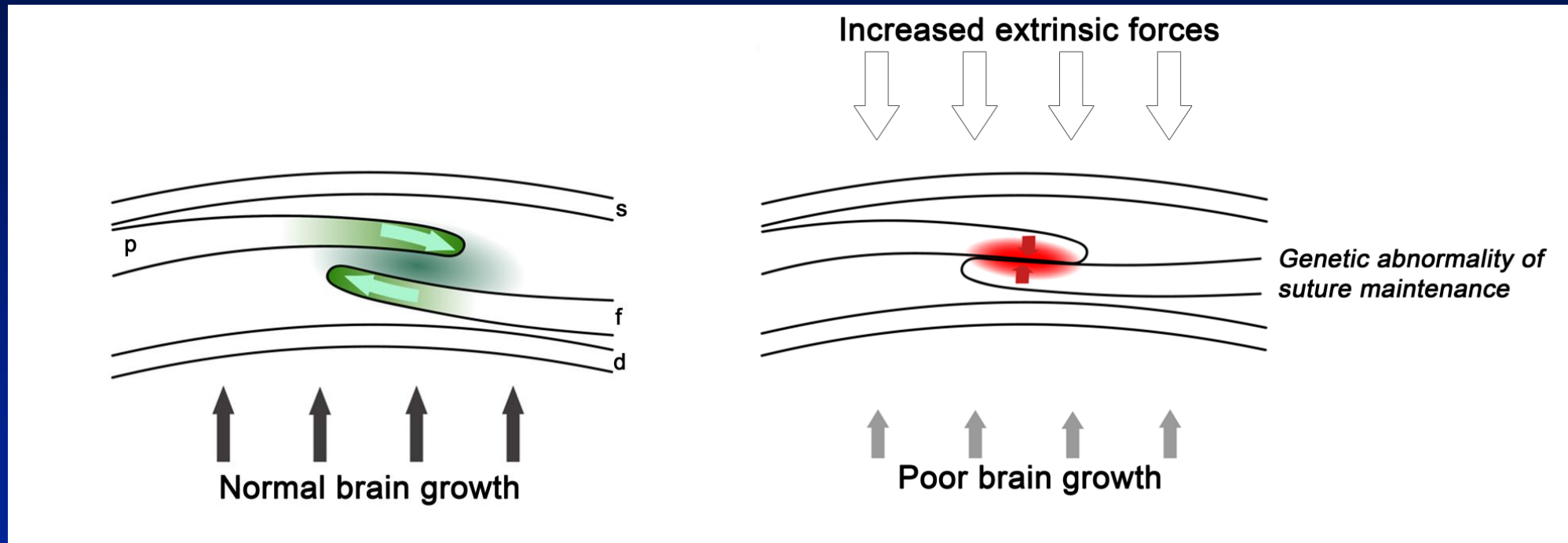
Helen Brittain (Birmingham)
Kerra Templeton (Glasgow)
Debbie Shears, Andrew Wilkie (Oxford)
Astrid Weber, Siva Sithambaram (Liverpool)
Louise Wilson, Lara Menzies (Great Ormond Street)

Posterior craniectomy in cloverleaf skull



Courtesy of David Johnson

How does craniosynostosis occur?



Environmental, polygenic and monogenic/ chromosomal factors all contribute to craniosynostosis

RESEARCH ARTICLE

AMERICAN JOURNAL OF
medical genetics PART
A

Fetal Constraint as a Potential Risk Factor for Craniosynostosis

Pedro A. Sanchez-Lara,^{1*} Suzan L. Carmichael,² John M. Graham Jr.,³ Edward J. Lammer,⁴ Gary M. Shaw,^{2,5} Chen Ma,² Sonja A. Rasmussen⁶
and the National Birth Defects Prevention Study

TABLE III. Summary of Constraint-Related Factors for all Suture Types Combined, the National Birth Defects Prevention Study, 1997–2004*

Characteristics	No. cases	No. controls	OR (95% CI) crude	No. cases	No. controls	OR (95% CI) adjusted ^a
Plurality						
Singleton	637	5,726	Reference	592	4,950	Reference
Twin or higher order	32	141	2.0 [1.4–3.0]	29	125	1.4 [0.9–2.3]
Birth weight						
Low birth weight	45	269	1.7 [1.2–2.3]	41	227	1.9 [1.3–2.7]
Normal weight	485	4,882	Reference	450	4,221	Reference
Macrosomia	88	613	1.4 [1.1–1.8]	82	535	1.1 [0.9–1.5]
Gestational age						
Preterm	84	470	1.7 [1.3–2.2]	80	399	1.9 [1.5–2.5]
Term	542	5,210	Reference	504	4,518	Reference
Prolonged	12	106	1.1 [0.6–2.0]	9	83	1.0 [0.5–2.1]
Parity						
No prior birth	230	2,302	0.9 [0.7–1.1]	210	1,988	1.0 [0.8–1.3]
One	229	1,947	1.0 [0.8–1.3]	214	1,690	1.1 [0.9–1.3]
2 or more	176	1,520	Reference	168	1,321	Reference

*All analyses excluded mothers with prepregnancy diabetes and all analyses except those of plurality also excluded multiple births.

^aAll adjusted models included maternal body mass index, education, race–ethnicity, age, fertility treatments, infant sex, gestational diabetes, and smoking.

Environmental, polygenic and monogenic/ chromosomal factors all contribute to craniosynostosis

PEDIATRIC/CRANIOFACIAL

Genetic and Epigenetic Influences of Twins on the Pathogenesis of Craniosynostosis: A Meta-Analysis

Gregory E. Lakin, M.D.
Jeremy C. Sinkin, M.D.
Rui Chen, Ph.D.
Peter F. Koltz, M.D.
John A. Giroto, M.D.,
M.M.A.

Background: The pathoetiology of craniosynostosis is not well understood. It likely results from a combination of genetic and epigenetic phenomena, such as intrauterine constraint from multiple gestations. Information on craniosynostosis in twins is limited to case reports and series. The authors conducted a systematic review and meta-analysis of the literature to elucidate the genetic and nongenetic influences of twins on the pathogenesis of craniosynostosis.

patients, and representing a total of 199 twins with craniosynostosis. Twinning was 2.62 times greater in patients with craniosynostosis (6.29 percent) compared with unaffected controls (2.4 percent; $p < 0.0001$). Boys were affected more than girls (65.30 versus 34.70 percent, respectively; $p < 0.0001$). Monozygotic concordance rates were greater than dizygotic (60.90 versus 5.30 percent, respectively; $p < 0.0001$) but were not 100 percent. Phenotypic variability was present in 62 percent of monozygotic twin sets ($p < 0.05$).

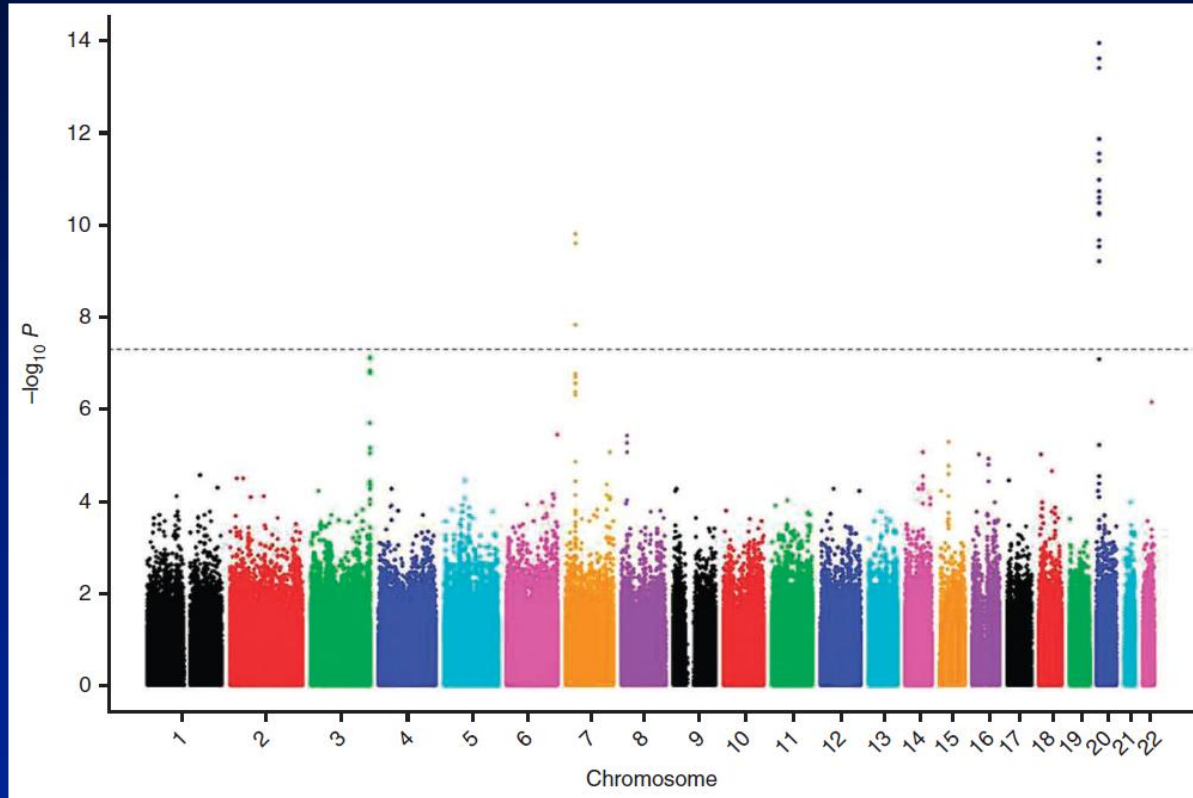
Environmental, polygenic and monogenic/ chromosomal factors all contribute to craniosynostosis

nature
genetics

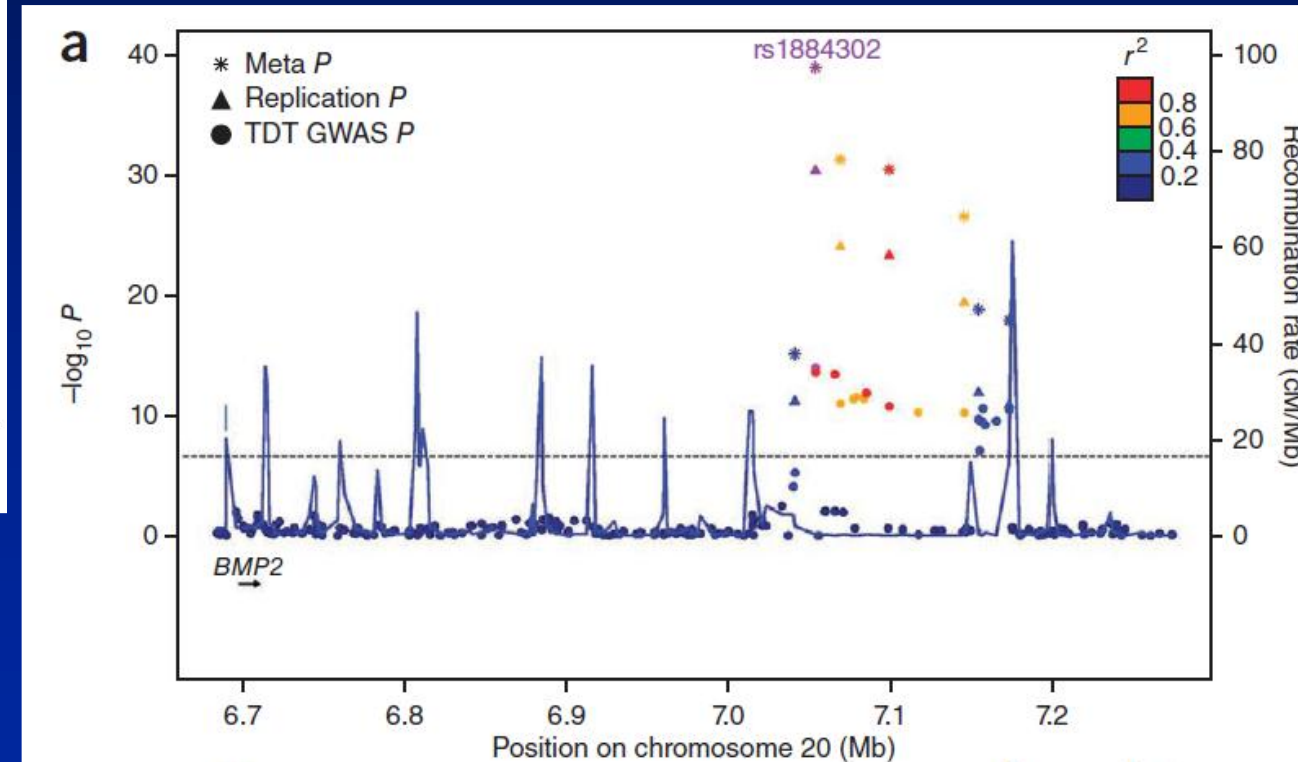
A genome-wide association study identifies susceptibility loci for nonsyndromic sagittal craniosynostosis near *BMP2* and within *BBS9*

Cristina M Justice^{1,24}, Garima Yagnik^{2,24}, Yoonhee Kim¹, Inga Peter³, Ethylin Wang Jabs³, Monica Erazo³, Xiaoqian Ye³, Edmond Ainehsazan³, Lisong Shi³, Michael L Cunningham⁴, Virginia Kimonis⁵, Tony Roscioli⁶, Steven A Wall⁷, Andrew O M Wilkie^{7,8}, Joan Stoler⁹, Joan T Richtsmeier¹⁰, Yann Heuzé¹⁰, Pedro A Sanchez-Lara¹¹, Michael F Buckley¹², Charlotte M Druschel¹³, James L Mills¹⁴, Michele Caggana¹⁵, Paul A Romitti¹⁶, Denise M Kay¹⁵, Craig Senders¹⁷, Peter J Taub¹⁸, Ophir D Klein^{19–21}, James Boggan²², Marike Zwienenberg-Lee²², Cyrill Naydenov²³, Jinoh Kim², Alexander F Wilson¹ & Simeon A Boyadjiev²

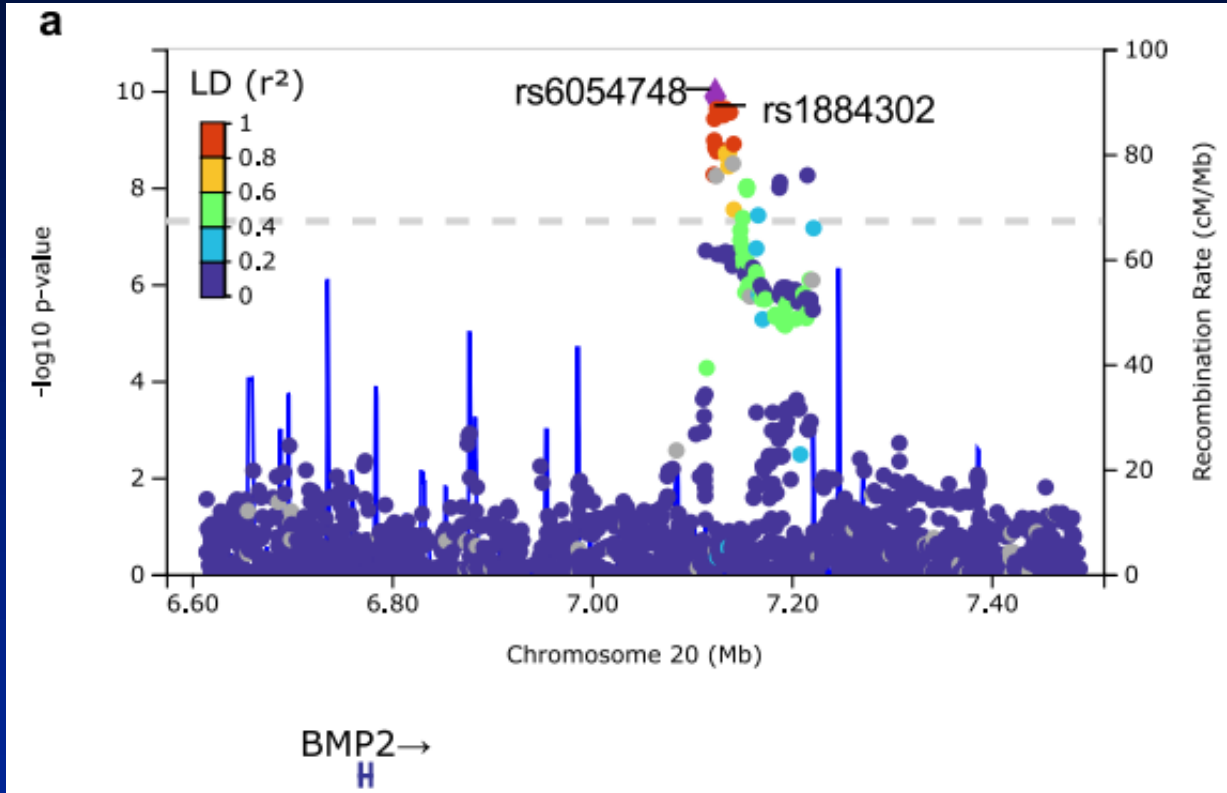
Environmental, polygenic and monogenic/ chromosomal factors all contribute to craniosynostosis



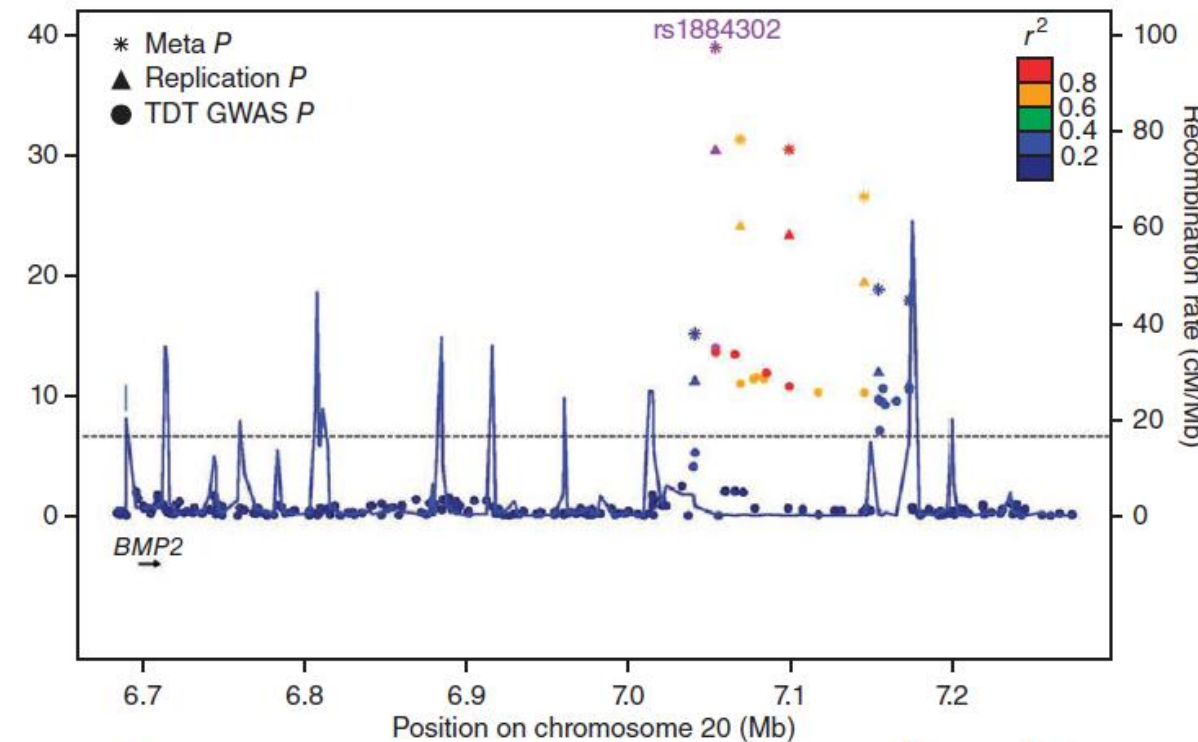
GWAS of sagittal craniosynostosis



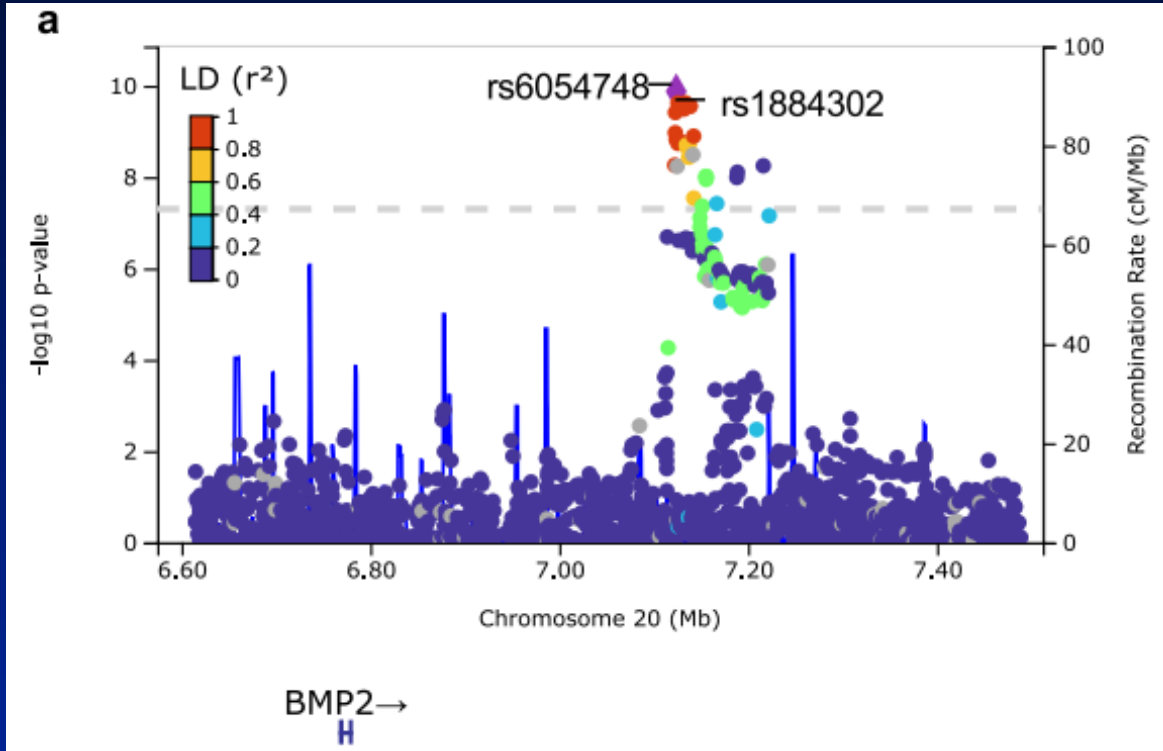
Environmental, polygenic and monogenic/ chromosomal factors all contribute to craniosynostosis



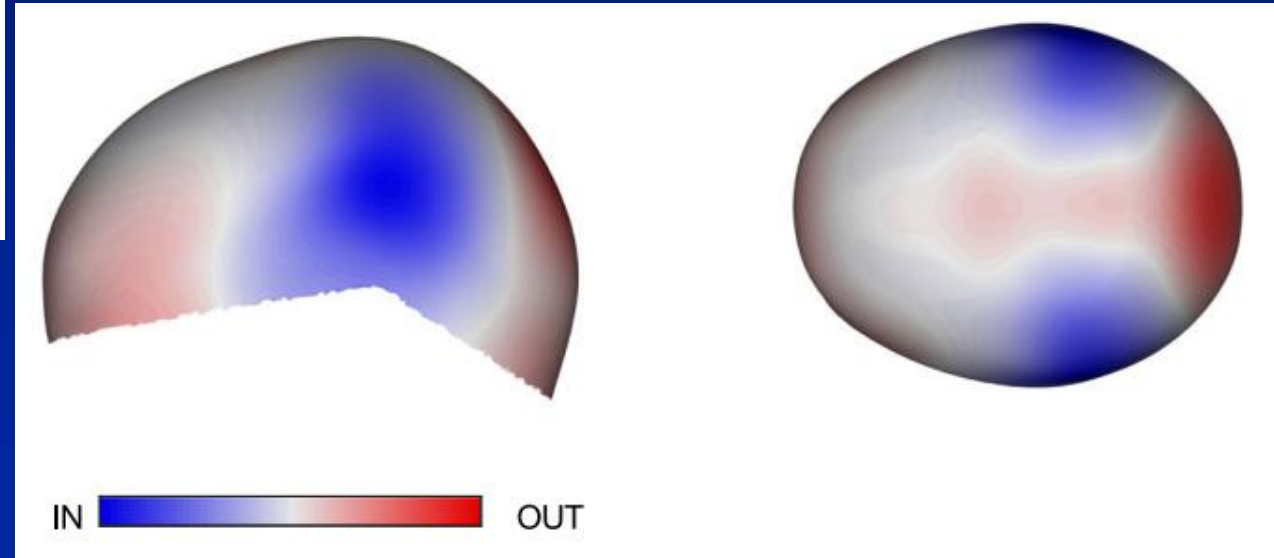
GWAS of cranial vault shape

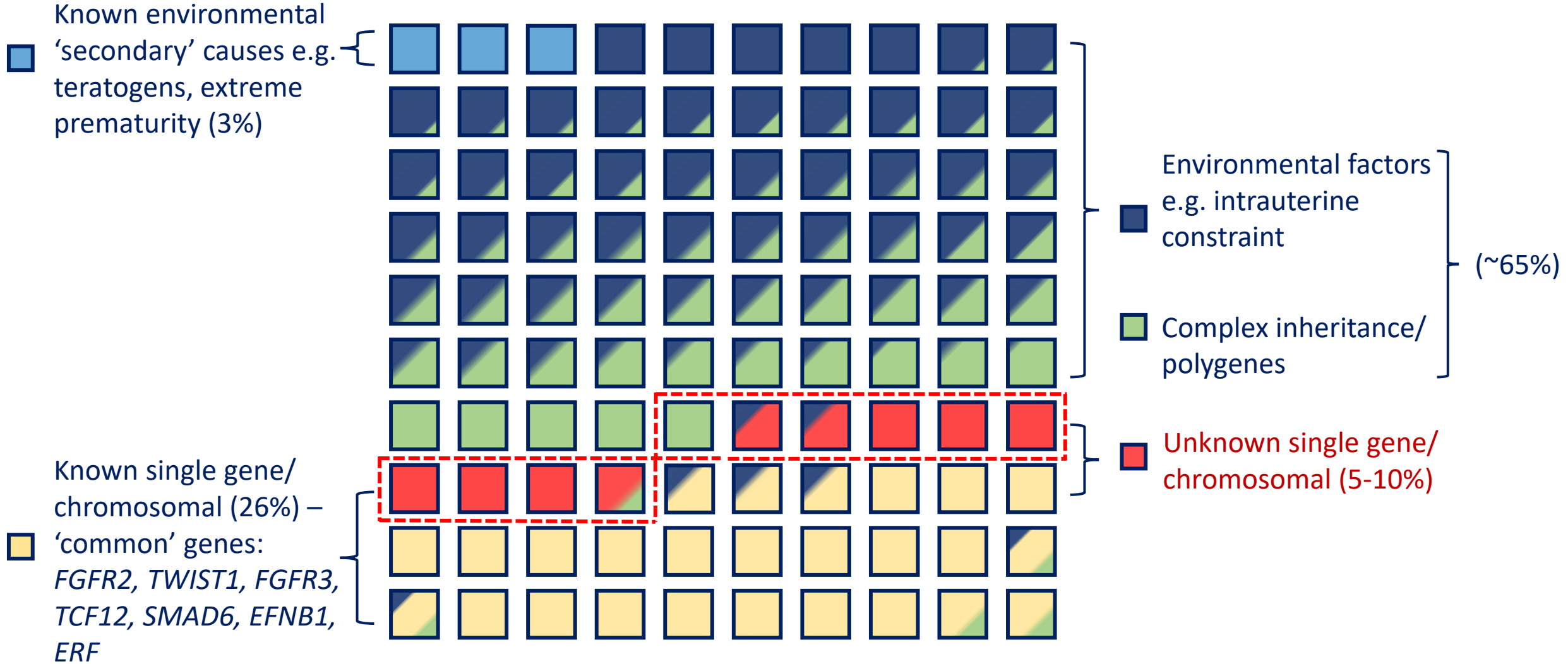


Environmental, polygenic and monogenic/ chromosomal factors all contribute to craniosynostosis

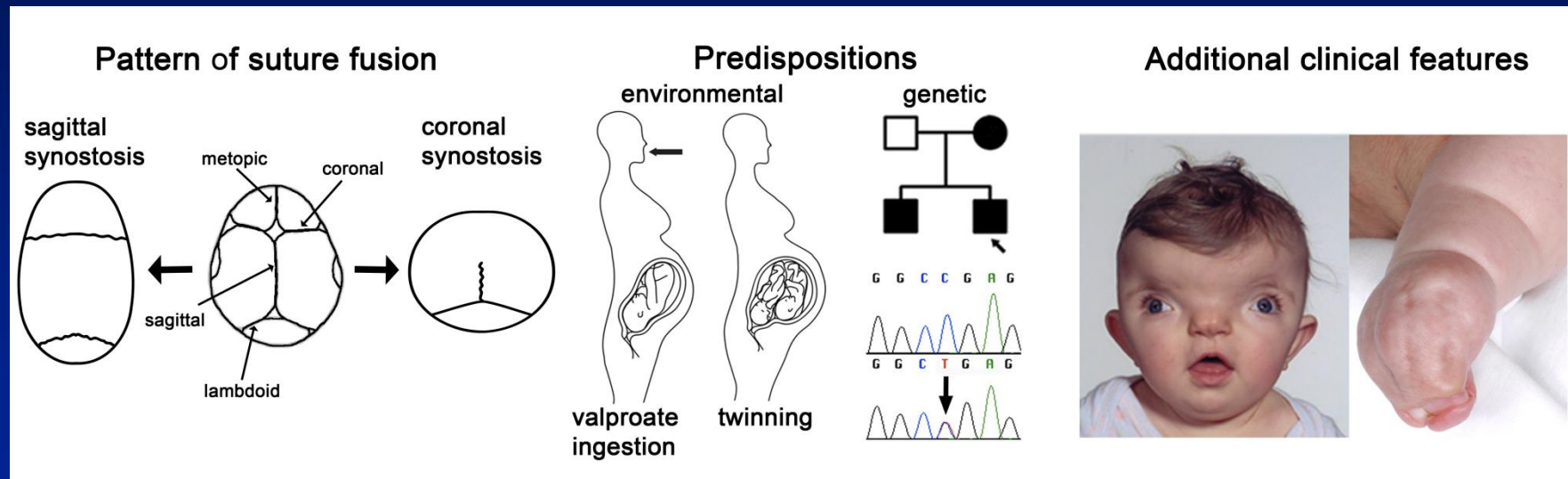


GWAS of cranial vault shape

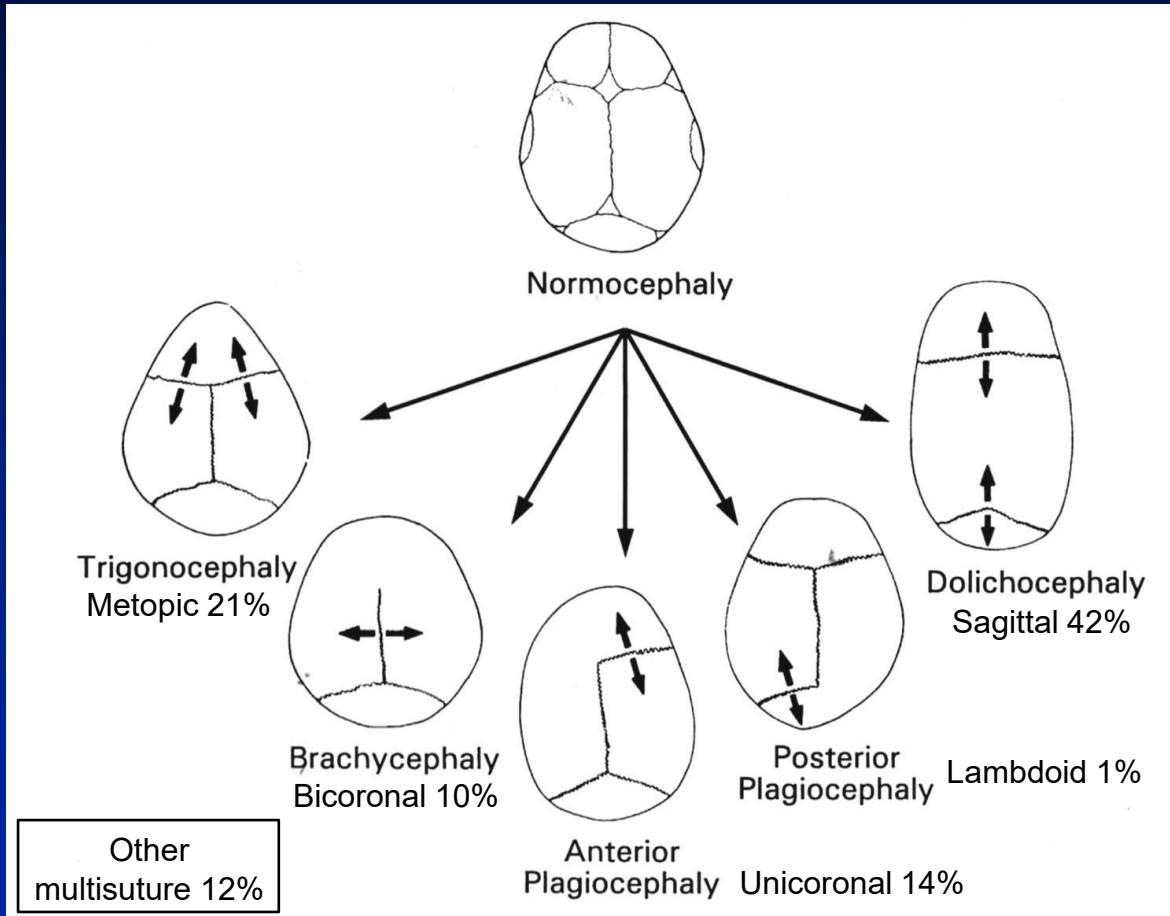




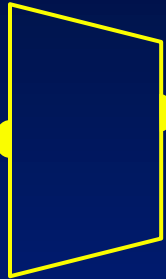
History and examination aims to uncover causative factors



Assessment of skull shape



Anterior plagiocephaly (flattening R brow)



R unicoronal craniosynostosis

Anterior plagiocephaly (flattening L brow)



Positional plagiocephaly

Oxford birth cohort study: 13-year data

N=666; 24% overall genetic diagnoses

REVIEW

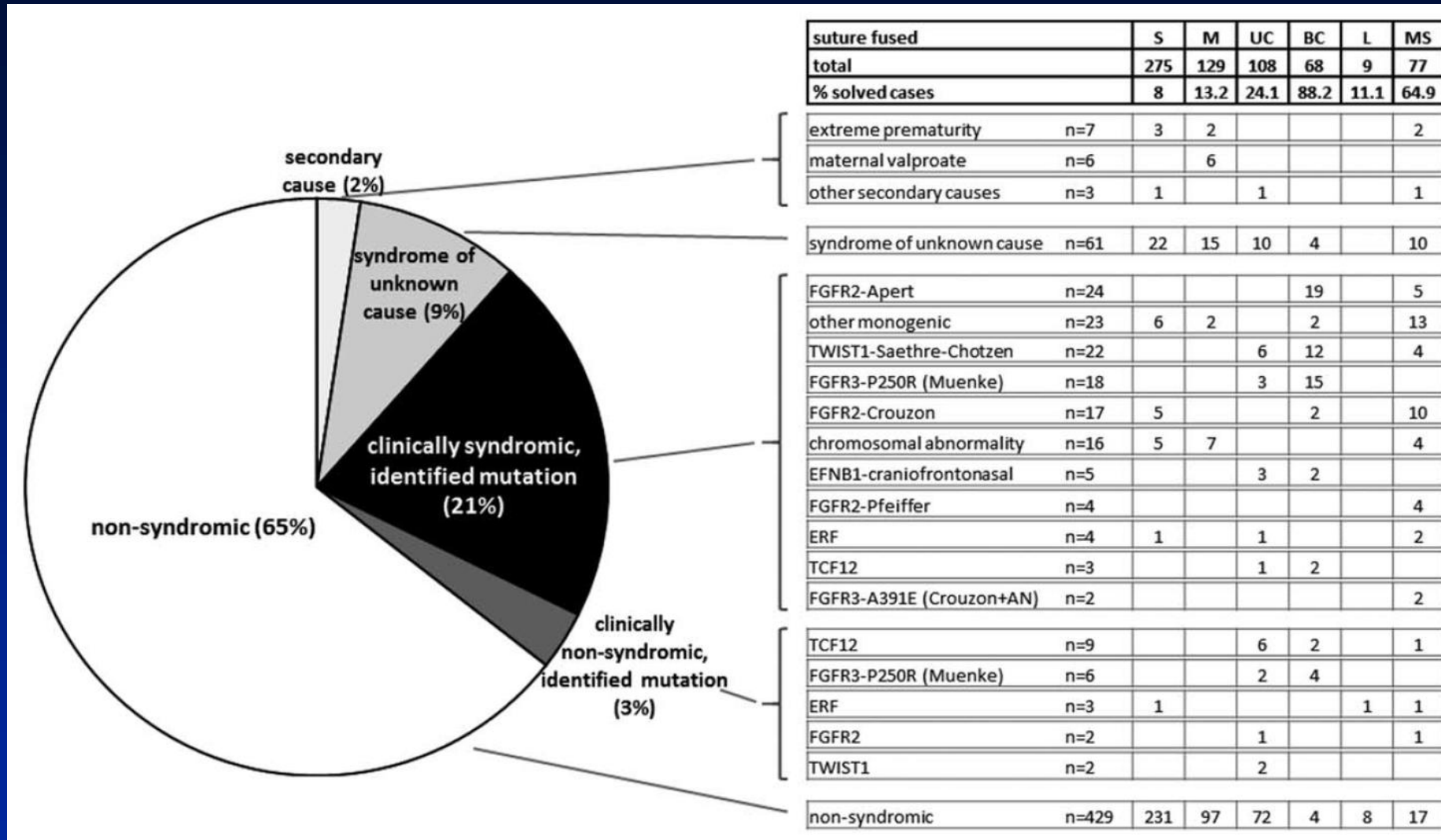


Clinical genetics of craniosynostosis

Andrew O.M. Wilkie^{a,b,c}, David Johnson^c, and Steven A. Wall^c

Oxford birth cohort study: 13-year data

N=666; 24% overall genetic diagnoses



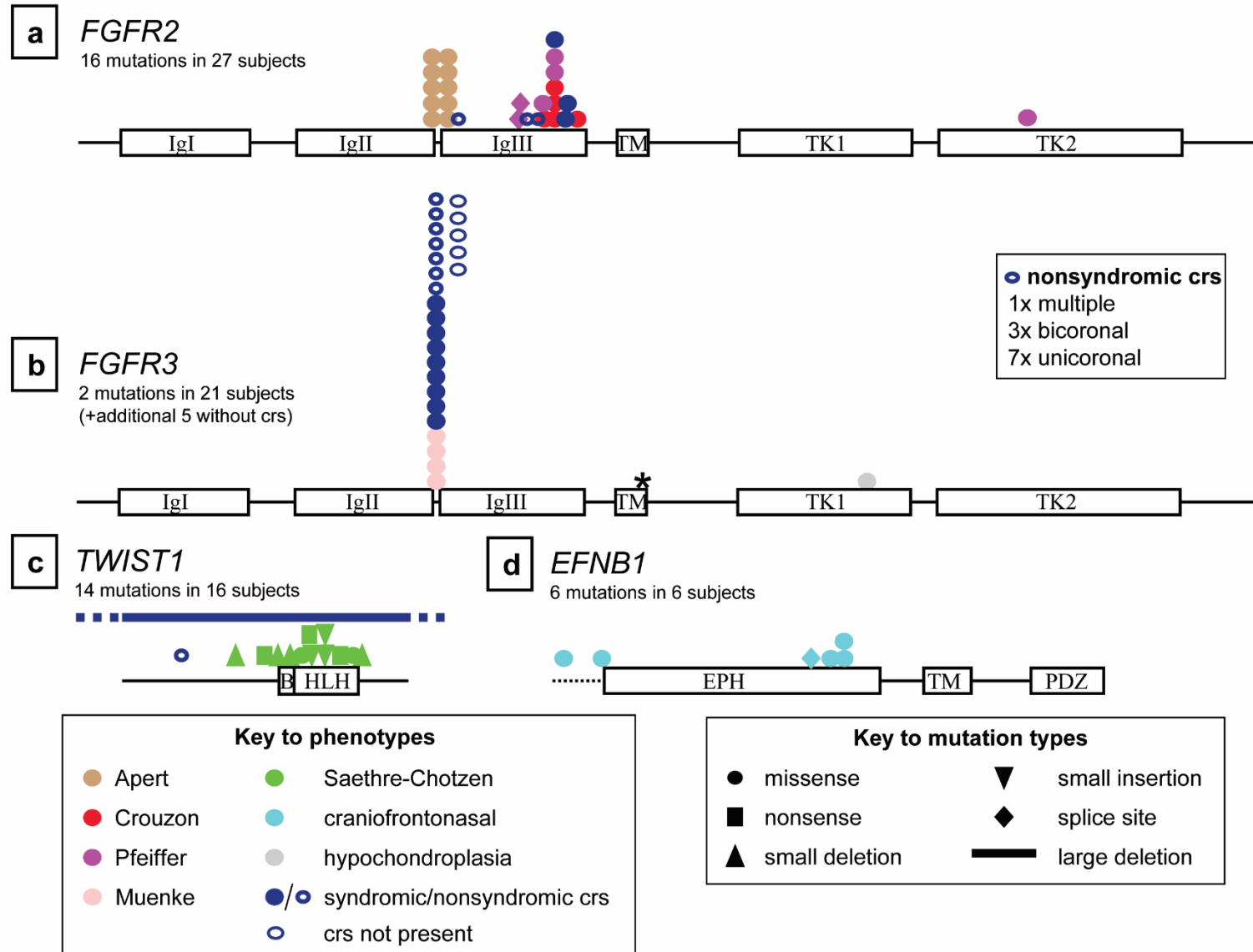
Genetic/biochemical mechanisms of craniosynostosis

Recessive
causes are
rare

Table 2. Biochemical Mechanisms in Craniosynostosis and Relationship to Pattern of Mendelian Inheritance

Biochemical Mechanism (and Pattern of Mendelian Inheritance)	Example Genes	Example Alleles	Comments	References
Complete loss of function (recessive)	<i>RAB23, IL11RA</i>	homozygous nonsense or frameshifting mutations; also aa substitutions	consanguinity leading to autozygosity frequent	41,44
Partial loss of function (recessive; hypomorphic mutation)	<i>POR, MEGF8, CDC45</i>	missense, weak splice site mutations (outside invariant aa and /gt sequences)	consanguinity leading to autozygosity occasional. Leaky mutations in essential genes; combinations of compound heterozygous alleles give more opportunity for combined output to fall within narrow window of activity for phenotypic effect	23,42,83,84,89
Partial loss of function (dominant; haploinsufficiency)	<i>TWIST1, TCF12, ERF</i>	complete and partial deletions; nonsense, frameshift; some aa substitutions	pathogenic aa substitutions localized to key DNA binding/dimerization regions. Biochemical and genetic evidence of interaction between <i>Twist1</i> and <i>Tcf12</i>	26,48,73
Partial loss of function (dominant negative)	<i>STAT3</i>	aa substitutions	aa substitutions cluster in SH2 or DNA binding domains	101
Gain of function: increased ligand affinity/broadened specificity (dominant)	<i>FGFR1, FGFR2, FGFR3</i>	equivalent Pro>Arg substitutions in IgII-IgIII linker of FGFR1, -2, and -3	substitution to bulky arginine residue introduces additional contacts to FGFRs, causing increased binding affinity and illegitimate binding by FGF10	102-106
	<i>MSX2</i>	Pro>His and Pro>Leu substitutions at 7 th position of MSX2 homeodomain	contacts minor groove of DNA, associated with altered DNA-binding specificity	107
Gain of function: constitutive activation (dominant)	<i>FGFR2, FGFR3</i>	aa substitutions to or from cysteine	results in covalent cross-linking of receptor monomers	108,109
	<i>FGFR2, FGFR3</i>	aa substitutions in kinase domain	abrogates requirement for dimerization	110
	<i>FGFR3</i>	aa substitutions near membrane-spanning region	enhances transient interactions between monomers	111
	<i>ZIC1</i>	loss of inhibitory motif	enhanced transcriptional activation	52,65,66
Gain of function: increased dosage (dominant)	<i>MSX2, IHH, RUNX2</i>	complete gene or regulatory element duplications	opposite phenotype (reduced ossification) associated with deletions in <i>MSX2</i> and <i>RUNX2</i> further illustrating dosage sensitivity	40,46,112
Gain of function: ectopic isoform expression (dominant)	<i>FGFR2</i>	deletions or insertions involving exon encoding <i>FGFR2c</i> spliceform	drives illegitimate expression of <i>FGFR2b</i> in usually non-expressing tissues	74,113,114
Cellular interference (X-linked dominant with paradoxical male sparing)	<i>EFNB1</i>	partial and complete heterozygous deletions and missense substitutions associated with similar phenotypes in females	occurs in females owing to random X-inactivation of X-linked <i>EFNB1</i> ; secondary abnormality of receptor levels (EPHB2, EPHA4) demonstrated in mice	115,116

Pattern of mutations in craniosynostosis

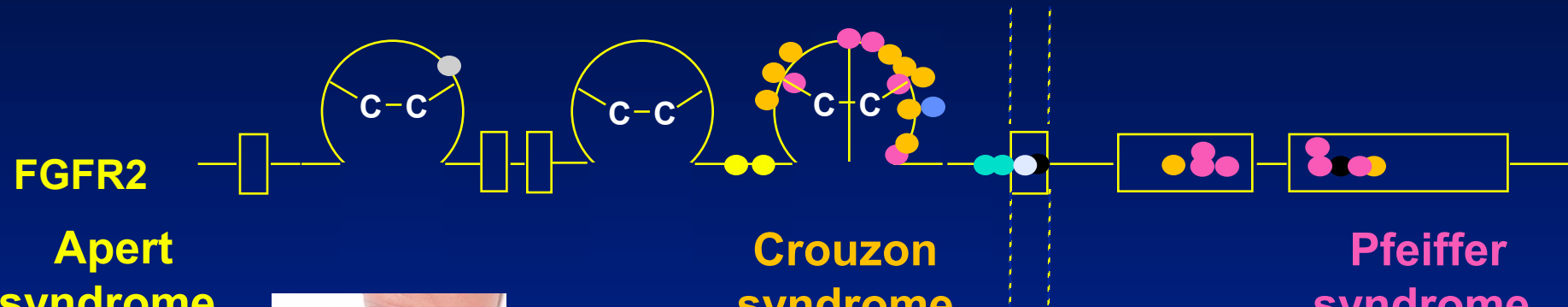


**FGFRs:
gain-of-function**

**Other Big 7:
loss-of-function**

FGFR2-related syndromes

- Pfeiffer
- Apert
- Beare-Stevenson
- Crouzon
- Jackson-Weiss
- Coronal synostosis
- Bent-bone dysplasia



Apert syndrome
(*n* = 30)



Crouzon syndrome
(*n* = 25)

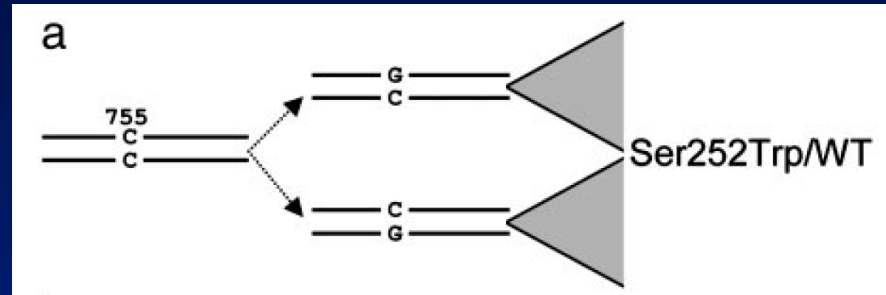


Pfeiffer syndrome
(*n* = 4)

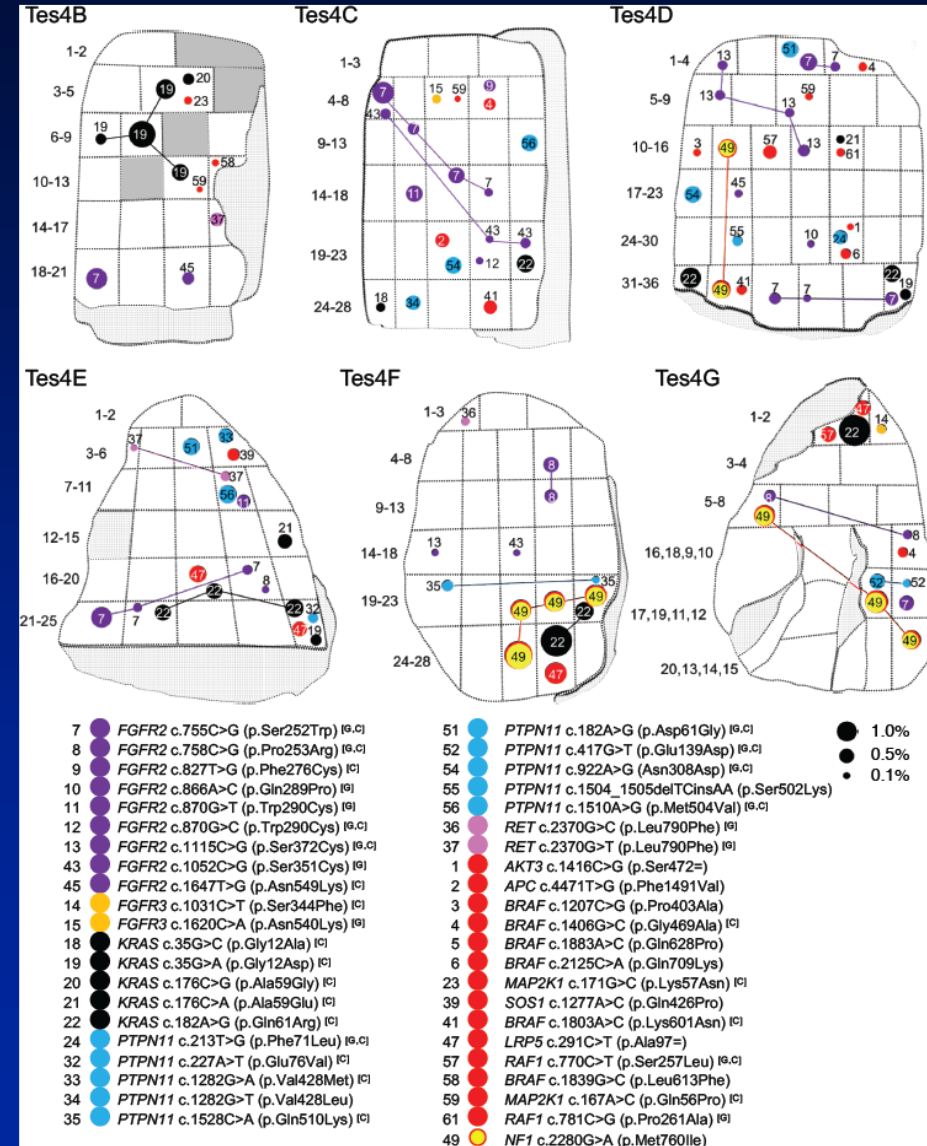


Why are Apert, Crouzon and Pfeiffer (*FGFR2*) and Muenke (*FGFR3*) syndromes so common?

Mutation Selection



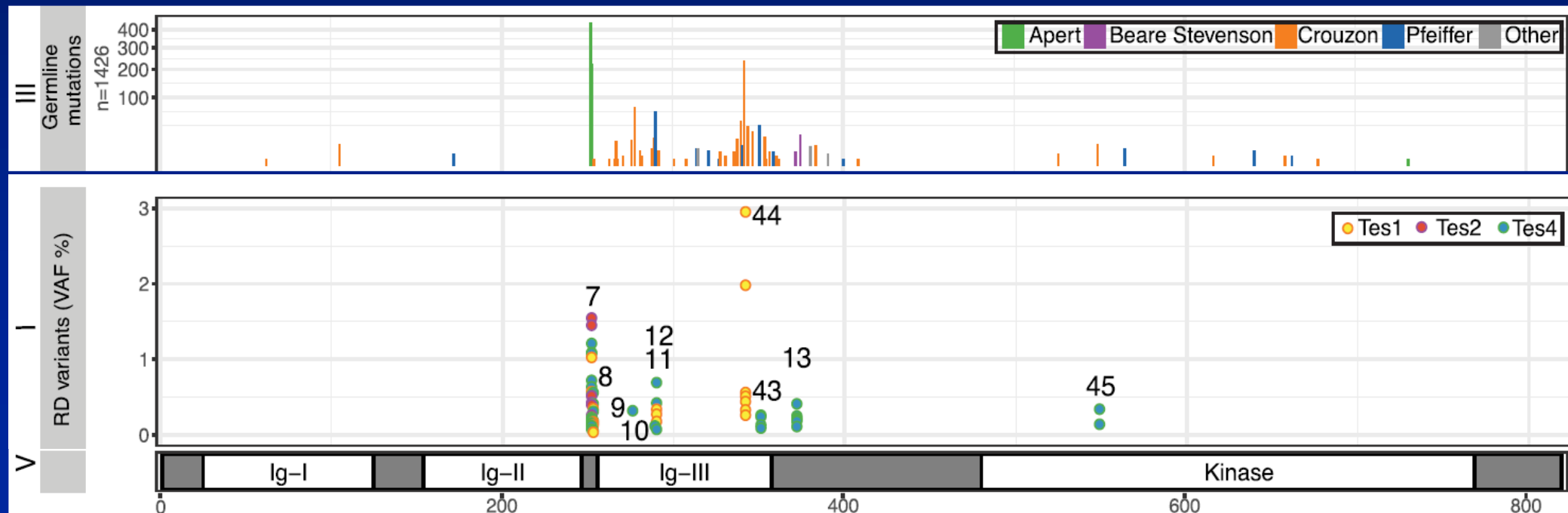
Selfish spermatogonial selection
(a process occurring in all men's testes as they get older)



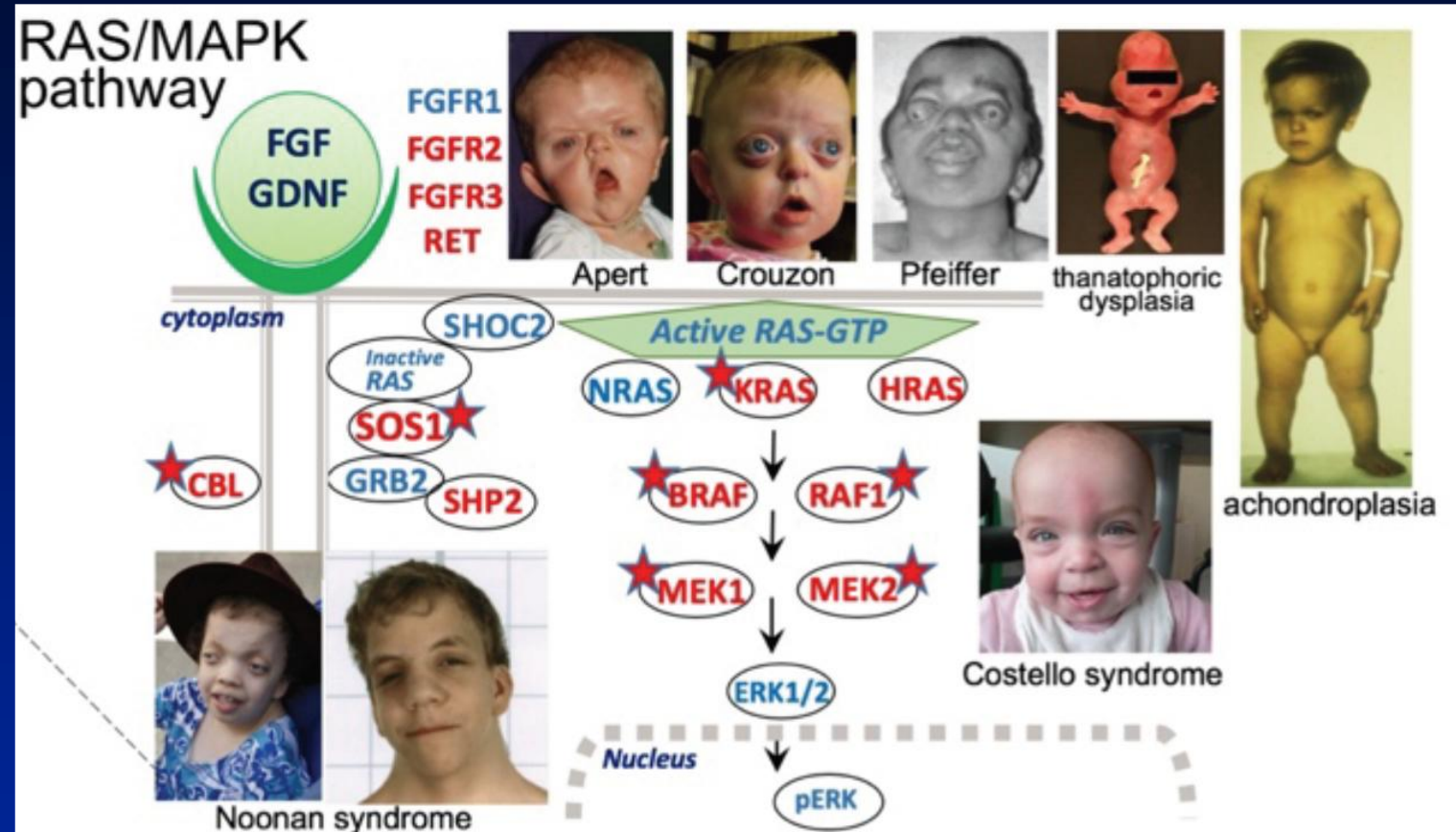
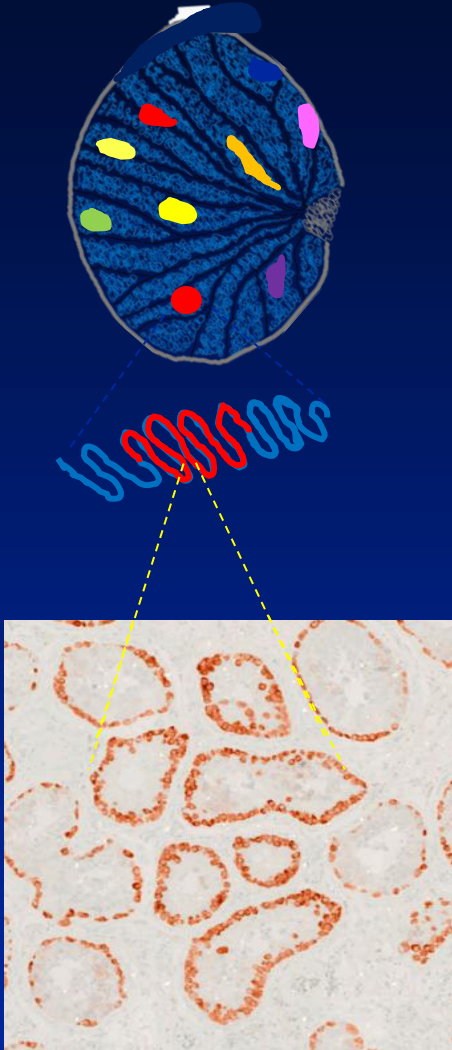
Cadaveric testis from 90 year old man

Why are Apert, Crouzon and Pfeiffer (*FGFR2*) and Muenke (*FGFR3*) syndromes so common?

Spectrum of *FGFR2* mutations in entire world literature, compared to those found in a single man's testis



Testes are factories of selfish mutations

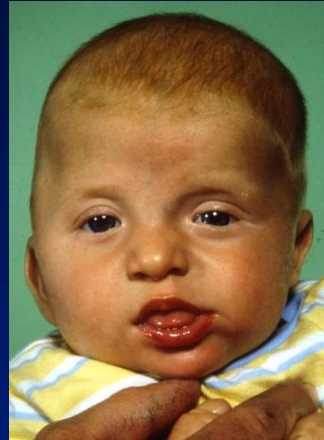


Although absolute *de novo* mutation levels are high, recurrence risks are **LOW**

Selfish mosaicism:
explains high frequency of FGFR mutations and RASopathies

Characteristic syndromes 2: Saethre-Chotzen syndrome (*TWIST1*)

$n = 31$
(+3 with N/S
presentation)



- missense
- ▼ duplication
- ▲ deletion
- ◆ nonsense



Saethre-Chotzen syndrome



Megabase-
scale deletions
in 7p21.1

Significant learning difficulties

Johnson et al, Am J Hum Genet (1998), Merrill et al Hum Mol Genet (2006)

Importance of long-term followup of individuals with *TWIST1* mutations

Reoperation for Intracranial Hypertension in *TWIST1*-Confirmed Saethre-Chotzen Syndrome: A 15-Year Review

Roger H. Woods, F.R.A.C.S.
Ehtesham Ul-Haq,
F.C.P.S. (Surg.)
Andrew O. M. Wilkie, D.M.,
F.R.C.P.
Jayaratnam Jayamohan,
F.R.C.S. (S.N.)
Peter G. Richards, F.R.C.S.
David Johnson, D.M.,
F.R.C.S. (Plast.)
Tracy Lester, Ph.D.,
F.R.C.Path.
Steven A. Wall, F.R.C.S.
Oxford, United Kingdom

Background: Saethre-Chotzen syndrome is a syndromic craniosynostosis defined by a genetic mutation affecting the *TWIST1* gene on chromosome 7p21. It is typically associated with unicoronal or bicoronal synostosis, eyelid ptosis, dysmorphic external ears, and other variable facial and limb abnormalities. Surgical management of the craniosynostosis addresses the calvarial deformity and may relieve or reduce the risk of intracranial hypertension. The aim of this study was to assess surgical intervention, with particular consideration of the reoperation rate for intracranial hypertension, in Saethre-Chotzen syndrome patients.

Methods: A retrospective case note analysis was performed on all patients with a confirmed *TWIST1* gene abnormality who attended the Oxford Craniofacial Unit over a 15-year period. Each patient's mutation and clinical features were recorded. Surgical intervention and sequelae were examined in greater detail.

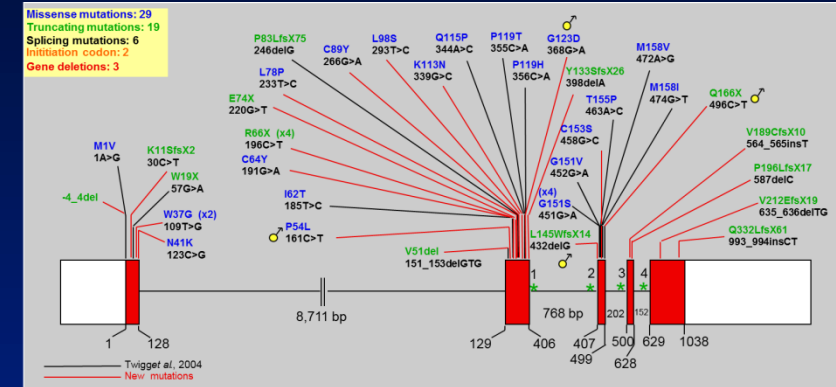
Results: Thirty-four patients with genetically confirmed Saethre-Chotzen syndrome were identified. All had craniosynostosis (bicoronal, 76 percent; unicoronal, 18 percent; bicoronal and sagittal, 6 percent), and the majority had eyelid ptosis, low frontal hairline, and external ear anomalies. Thirty-one patients had received surgical intervention. Nine of 26 patients (35 percent) with at least 12 months of follow-up after primary intervention and eight of 19 patients (42 percent) with at least 5 years of follow-up developed intracranial hypertension necessitating secondary calvarial surgery.

Conclusions: Despite standard surgical intervention, patients with Saethre-Chotzen syndrome have a high rate (35 to 42 percent) of recurrent intracranial hypertension necessitating further surgical expansion. All patients with either bicoronal synostosis or unicoronal synostosis with syndromic features should be screened for *TWIST1* mutations, as this confers a greater risk than nonsyndromic synostosis of the same sutures. Regular follow-up throughout the childhood years is essential. (Plast. Reconstr. Surg. 123: 1801, 2009.)

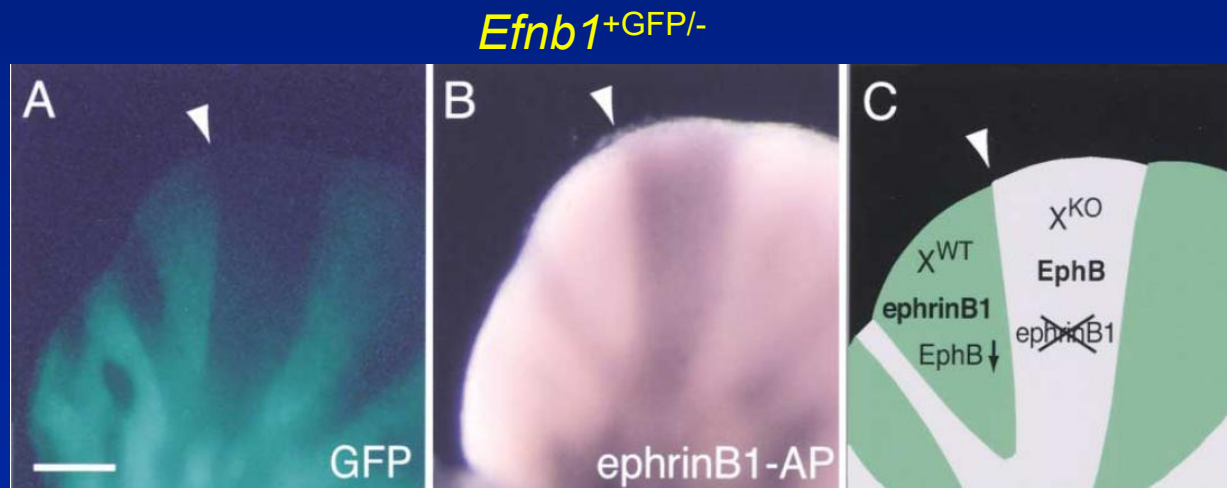
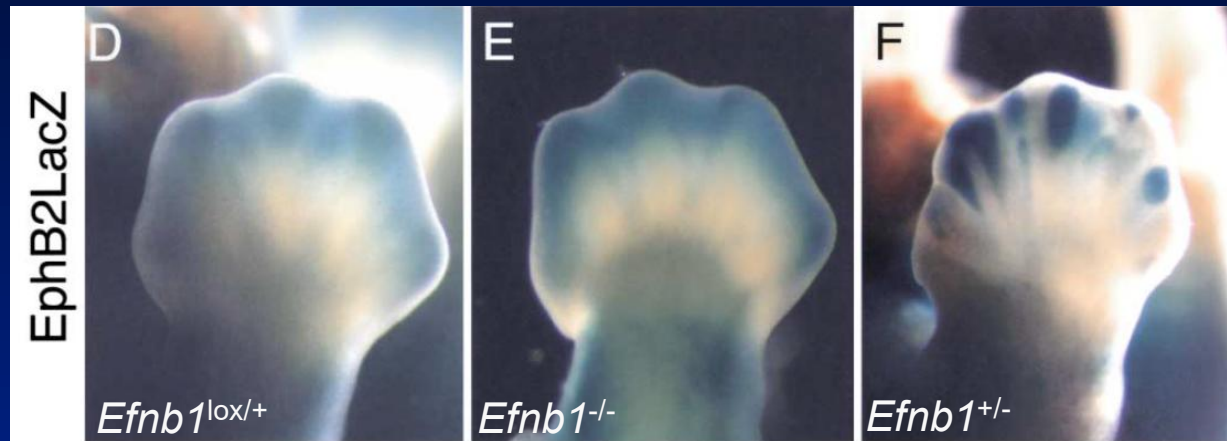


Characteristic syndromes 3: craniofrontonasal syndrome (*EFNB1*)

$n = 11$



Mosaicism (epigenetic, by X-inactivation, or genetic), creates abnormal tissue boundaries



Males mosaic for *EFNB1* mutations are more severely affected than hemizygotes

Cellular Interference

What are the other 2 X-linked disorders thought to be subject to cellular interference mechanism, leading to greater severity in females than males?

***PCDH19*-related epilepsy**

(DEVELOPMENTAL AND EPILEPTIC ENCEPHALOPATHY 9; DEE9; OMIM 300088) aka Juberg-Hellman syndrome

***ARR3*-related myopia**

(MYOPIA 26, X-LINKED, FEMALE-LIMITED; MYP26; OMIM 301010)

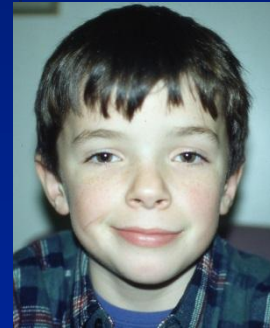
Syndromes defined by molecular diagnosis 1: *FGFR3*

Muenke $n = 23$ (+10 n/s presentation)

Crouzon AN $n = 4$



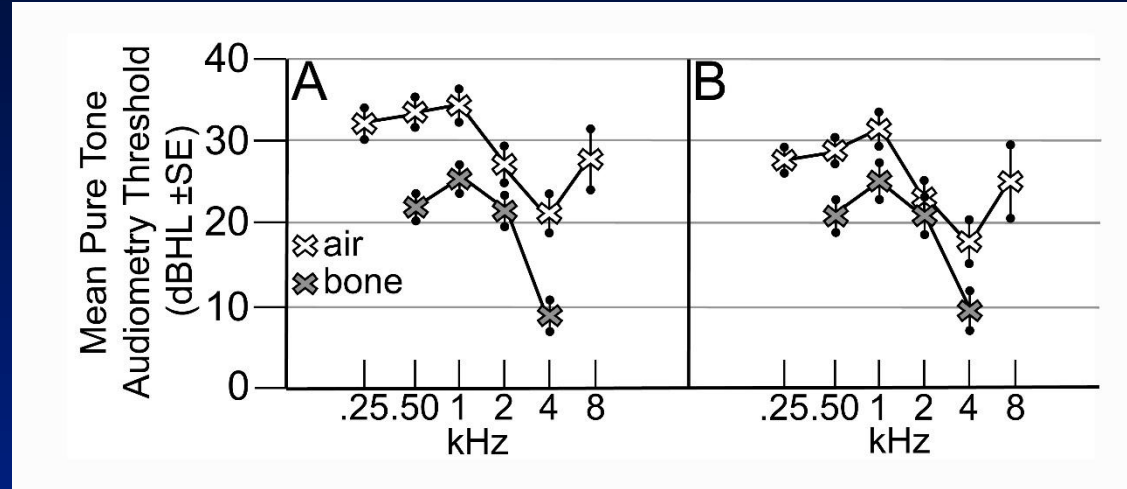
“nonsyndromic”
coronal synostosis
(Muenke syndrome,
P250R)



Crouzon syndrome
with acanthosis
nigricans (A391E)

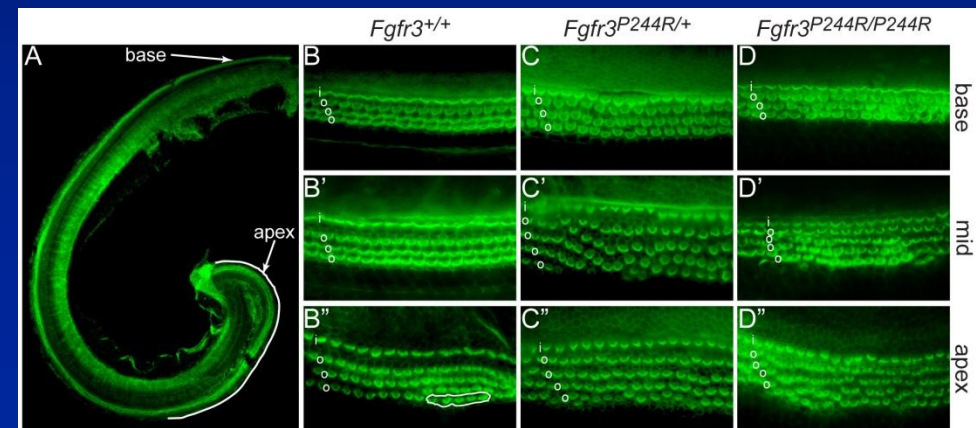
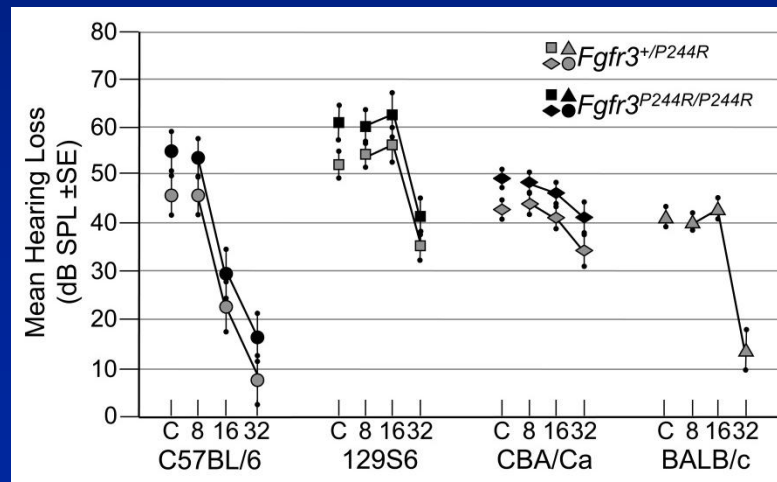


It is essential to screen for hearing loss in patients with Muenke syndrome



N = 37

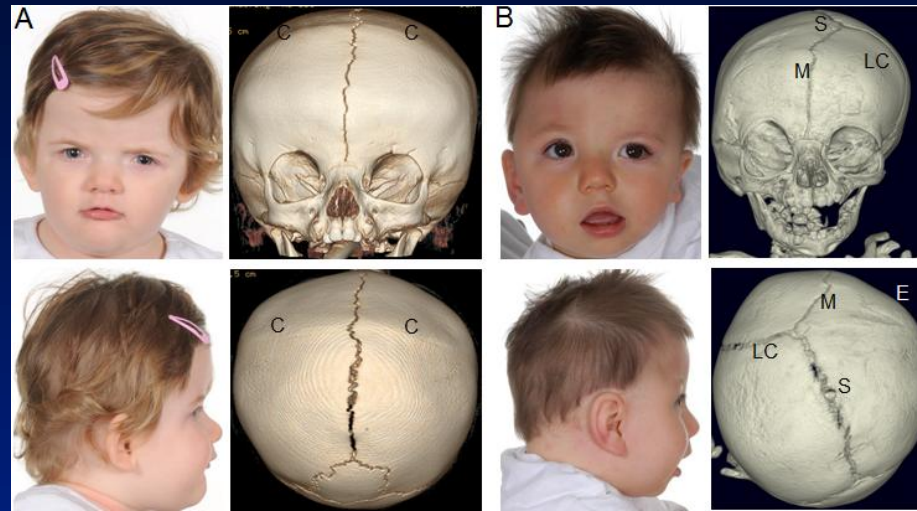
N = 41 ears from 30 subjects



Mansour et al Hum Mol Genet (2009)

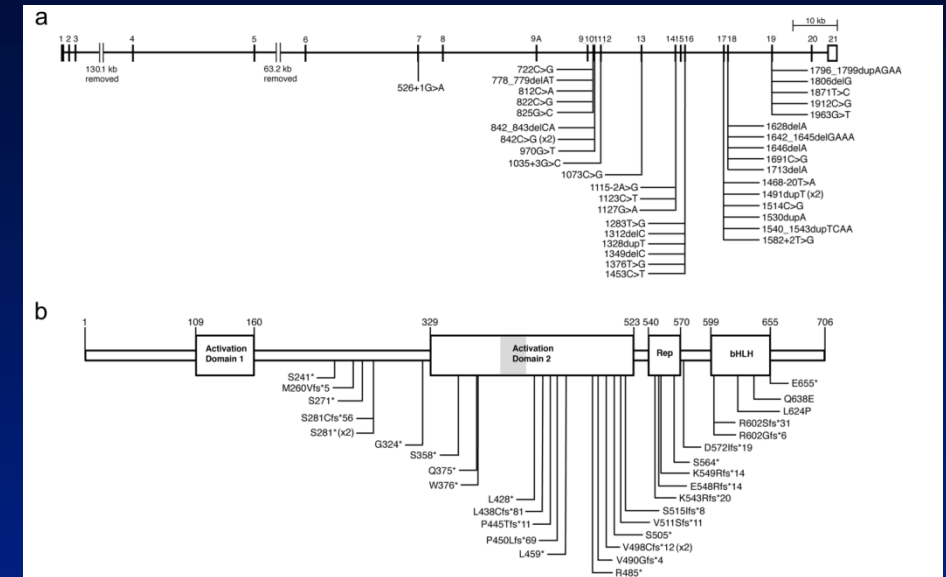
Syndromes defined by molecular diagnosis 2: *TCF12*

TCF12 $n = 16$
(6 syndromic,
10 n/s)



bicoronal

R unicoronal



Non-penetrance > 50%

Sharma et al *Nature Genet* (2013)

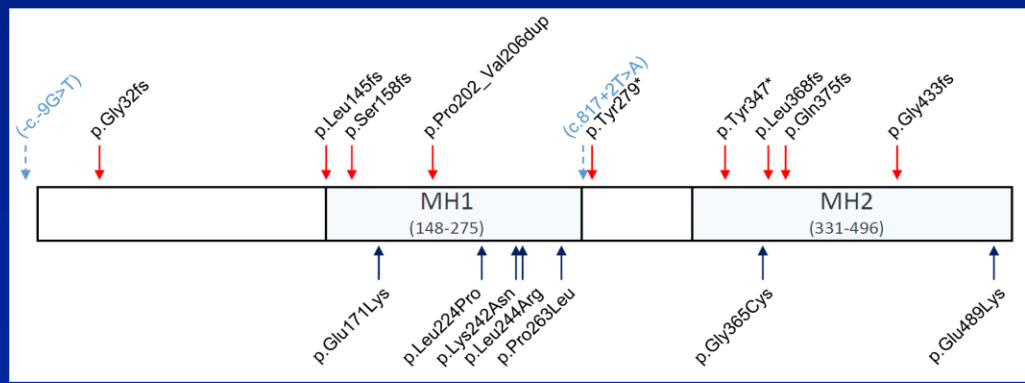
Syndromes defined by molecular diagnosis 3: *SMAD6*

SMAD6 n = 15
(3 syndromic,
12 n/s)

	Non-syndromic			Syndromic			Combined		
	Total	SMAD6 positive	%	Total	SMAD6 positive	%	Total	SMAD6 positive	%
Metopic	168	9	5.36	40	3	7.50	208	12	5.77
Sagittal	281	2	0.71	38	1	2.63	319	3	0.94
Unilateral coronal	149	1	0.67	14	0	0.00	163	1	0.61
Bilateral coronal	11	0	0.00	11	0	0.00	22	0	0.00
Uni- or bilateral lambdoid	7	0	0.00	3	0	0.00	10	0	0.00
Multisuture	36	1	2.78	30	1	3.33	66	2	3.03
Sutures not specified	0	0	0.00	11	0	0.00	11	0	0.00
Combined	652	13	1.99	147	5	3.40	799	18	2.25



Pre-op, aged 1 year 5 months



European Journal of Human Genetics
<https://doi.org/10.1038/s41431-019-0363-z>

ESHG

ARTICLE

Check for updates

Confirmation of the role of pathogenic *SMAD6* variants in bicuspid aortic valve-related aortopathy

Ilse Luyckx¹ · Gretchen MacCarrick² · Marlies Kempers³ · Josephina Meester¹ · Céline Geryl¹ · Olivier Rombouts¹ · Nils Peeters¹ · Charlotte Claes¹ · Nele Boeckx¹ · Natzi Sakalihan⁴ · Adeline Jacquinet⁵ · Alexander Hoischen^{3,6,7} · Geert Vandeweyer¹ · Sarah Van Lent¹ · Johan Saenen⁸ · Emeline Van Craenenbroeck⁸ · Janneke Timmermans⁹ · Anthonie Duijnhouwer⁹ · Harry Dietz^{2,10,11,12} · Lut Van Laer¹ · Bart Loeys^{1,3} · Aline Verstraeten¹

Received: 31 October 2018 / Revised: 22 January 2019 / Accepted: 24 January 2019

→Diagnosis should trigger cascade testing and echocardiographic screening
Timberlake et al *eLife*(2016), Calpena et al *Genet Med* (2021)

SMAD6 is a lot more complicated!

© American College of Medical Genetics and Genomics

ARTICLE

Genetics
in Medicine

Corrected: Correction



SMAD6 is frequently mutated in nonsyndromic radioulnar synostosis

Yongjia Yang, MS¹, Yu Zheng, MS¹, Wangming Li, BD², Liping Li, BD¹, Ming Tu, BD¹, Liu Zhao, BD¹, Haibo Mei, MD³, Guanghui Zhu, MD³ and Yimin Zhu, MD, PhD^{1,4}

SMAD6 is a lot more complicated!

Dataset gnomAD v4.1.0 gnomAD SVs v4.1.0 ?

Constraint ? Variant co-occurrence ?

Category	Expected SNVs	Observed SNVs	Constraint metrics
Synonymous	273.4	444	$Z = -5.62$ $o/e = 1.62 (1.5 - 1.76)$ 0 — 1
Missense	595.1	1102	$Z = -7.59$ $o/e = 1.85 (1.76 - 1.94)$ 0 — 1
pLoF	34.8	97	$pLI = 0$ $o/e = 2.79 (1.83 - 2)$ 0 — 1

Note

 More pLoF variants than expected

Note

 More missense variants than expected

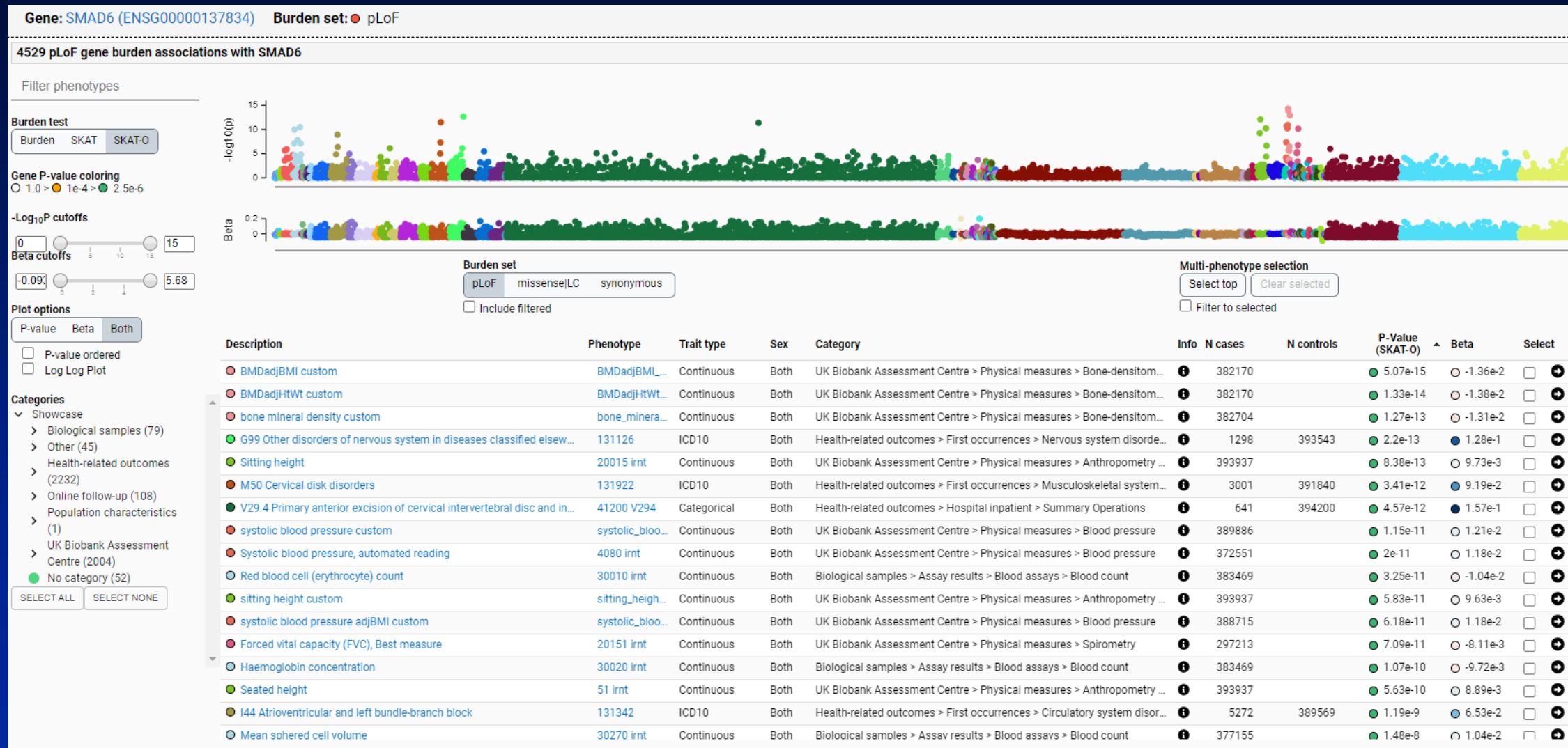
Note

 More or fewer synonymous variants than expected

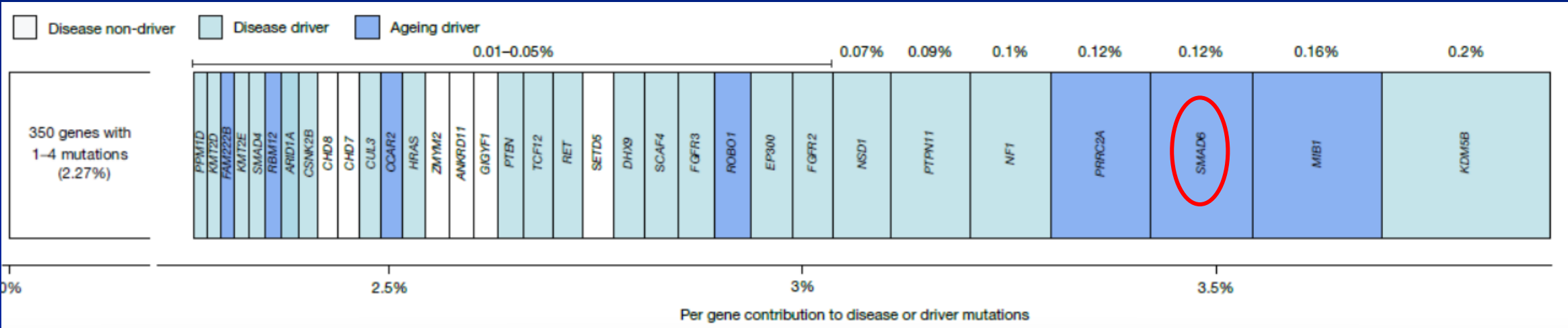
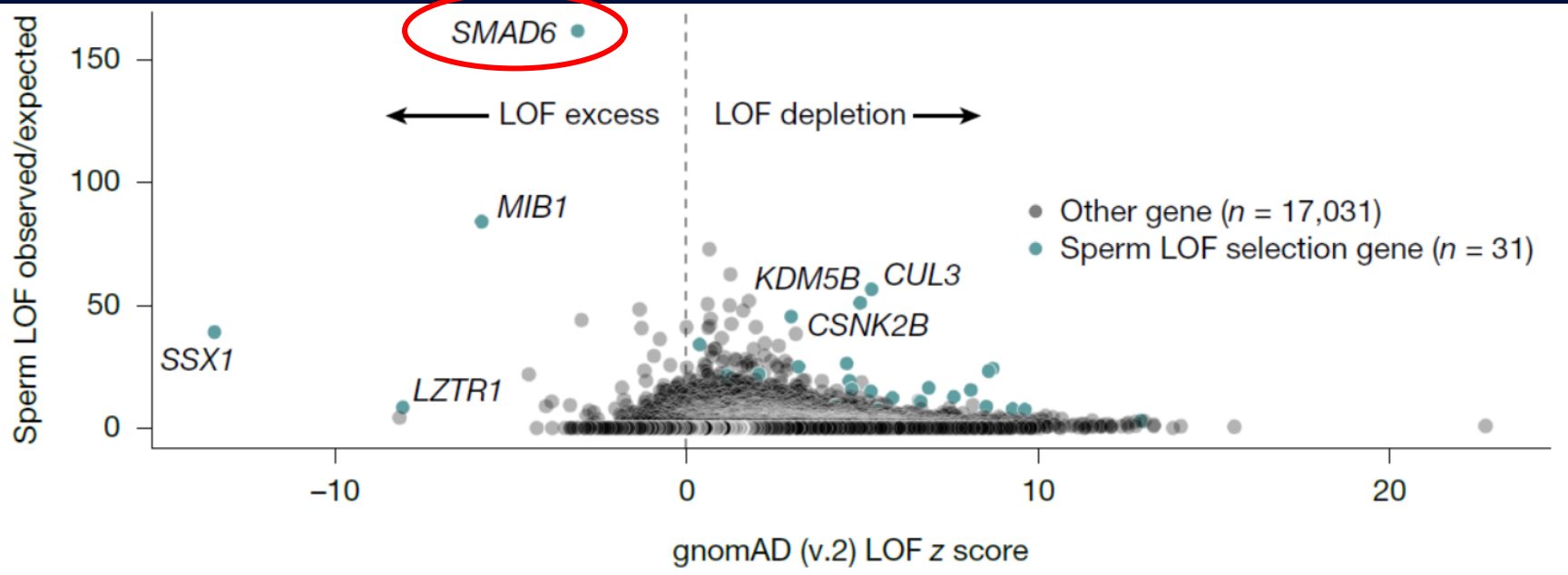
[More information on constraint flags.](#)

Constraint metrics based on MANE Select transcript (ENST00000288840.10).

SMAD6 is a lot more complicated!

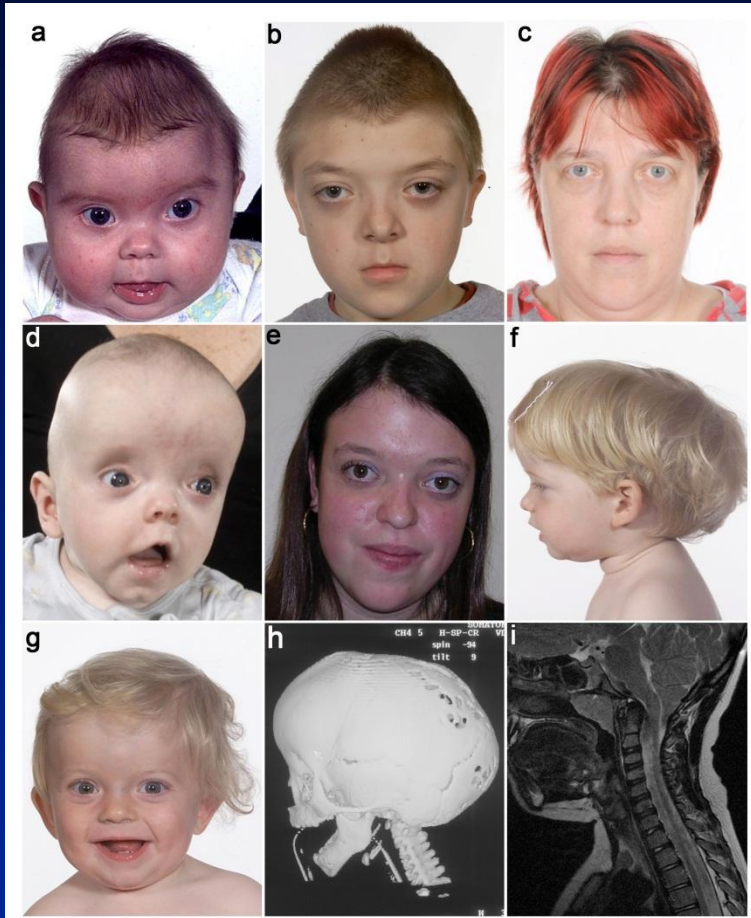


Positive selection of *SMAD6* mutations in sperm



Syndromes defined by molecular diagnosis 4: *ERF*

ERF $n = 9$
(6 syndromic,
3 n/s)

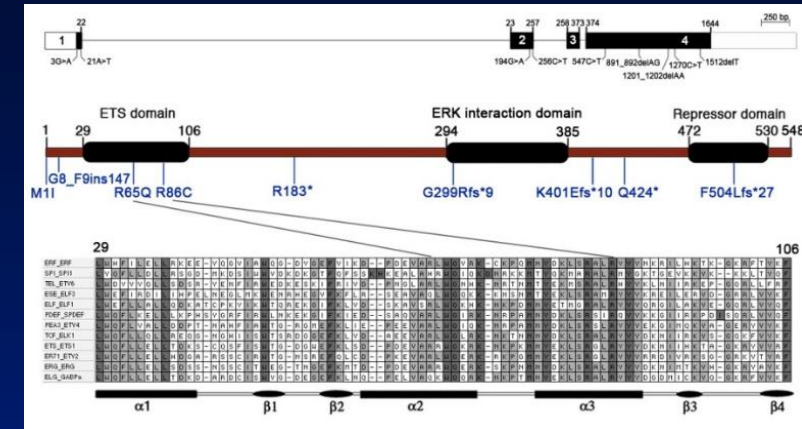


Some individuals present with
Noonan-like features (but
cardiac problems rare)

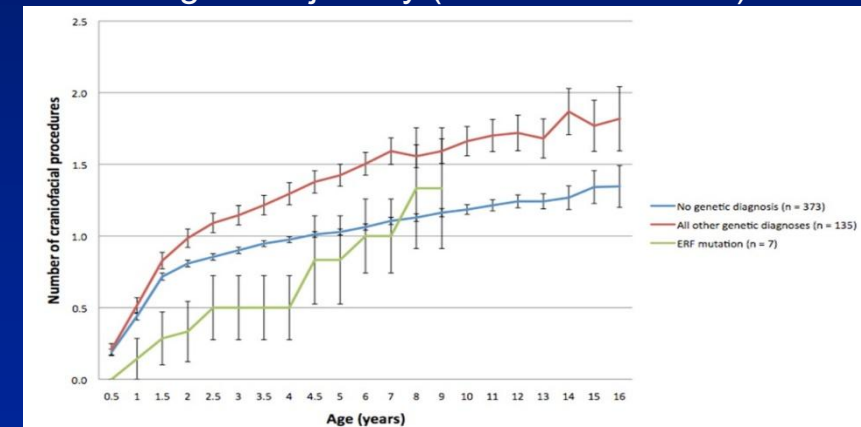
13 paediatric cases:

Chiari I malformation:
Pathologically raised ICP:
Speech delay/behavioural problems

4
9 cases (6 on ICP monitoring)
12 (verbal/non-verbal IQ discrepancy >25 in 3
Twigg et al Nature Genet (2013)

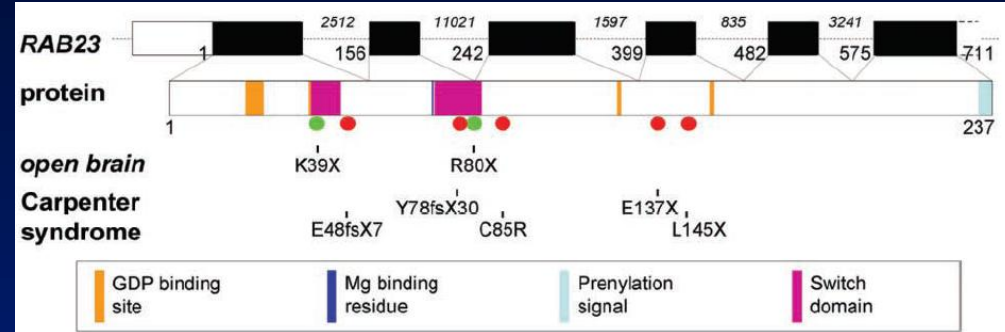
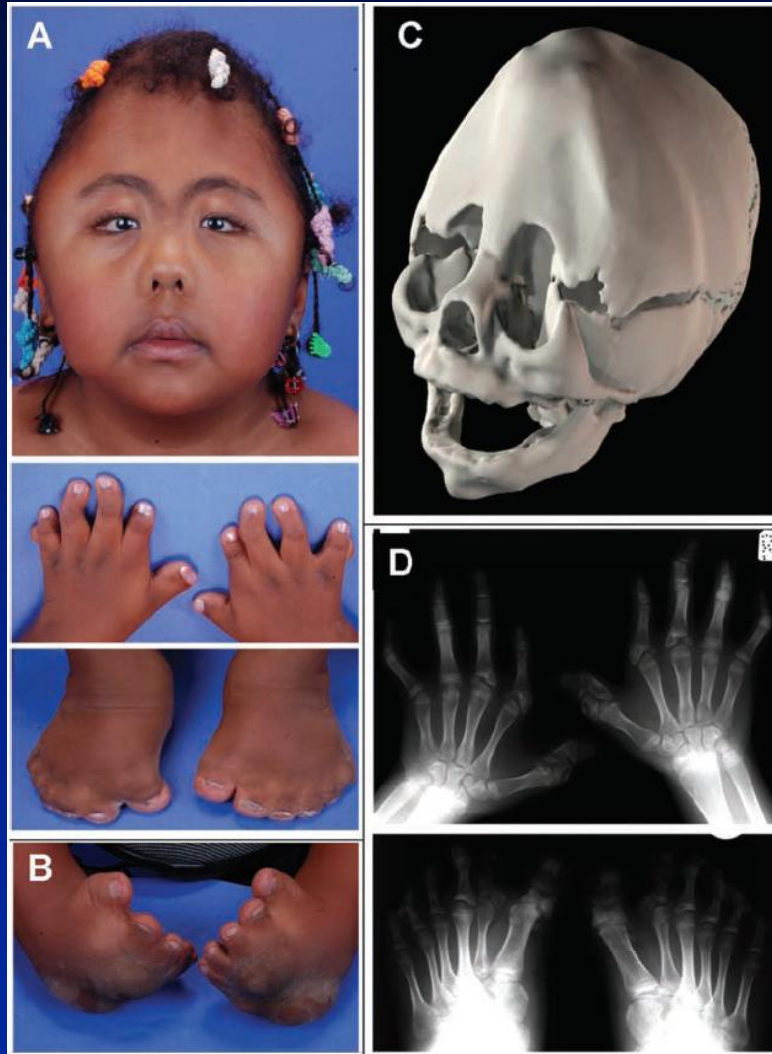


Surgical trajectory (n=7 Oxford cases)



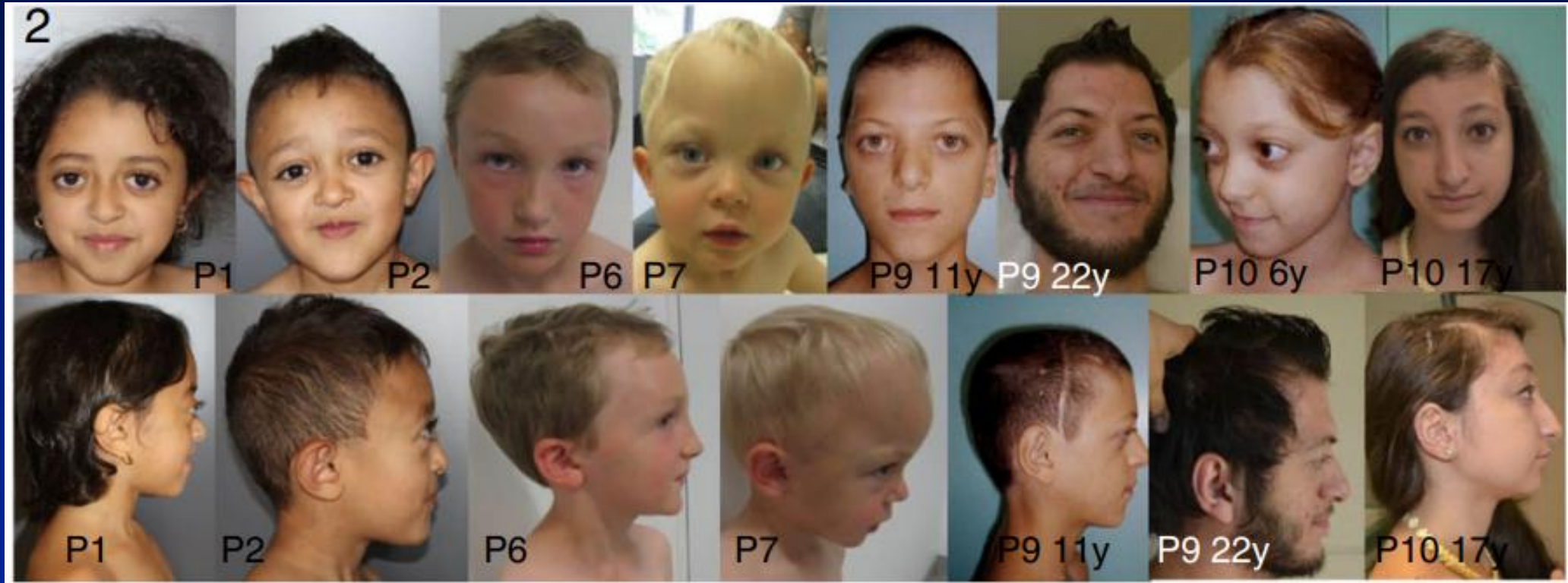
Recessive syndromes 1: Carpenter syndrome (*RAB23*, *MEGF8*)

$n = 0$



Recessive syndromes 2: *IL11RA*-related craniosynostosis

$n = 0$



Listed in OMIM as craniosynostosis and dental anomalies - CRSDA

Brischoux-Boucher *et al Clin Genet* (2018)

Implications for management with specific molecular diagnoses

TWIST1



Saethre-Chotzen syndrome

High rate
(35-42%)
recurrent
intracranial
hypertension

***Woods et al PRS
(2009)***

***FGFR3-
P250R***



Muenke syndrome

Sensorineural
hearing loss

***Mansour et al Hum
Mol Genet
(2009)***

***FGFR3-
A391E***



**Crouzon with
acanthosis
nigricans**

Hydrocephalus
Midface
hypoplasia
Acanthosis
nigricans

***De Planque et al J
Neurosurg Pediatr
(2021)***

ERF



***ERF-related
crs***

Late
presentation
with
pathologically
raised ICP

***Twigg et al
Nature
Genetics (2013)***

SMAD6



***SMAD6-
related crs***

Bicuspid
aortic valve
Ascending
thoracic
aortic
aneurysm

***Calpena et al
Genetics in Medicine
(2020)***

Gene Panels for Craniosynostosis (1)

R23 Apert syndrome

Testing Criteria

Clinical features strongly suggestive of Apert syndrome, including both craniosynostosis and syndactyly of the hands and feet, with or without additional features

Overlapping indications

- R306 NIPD for Apert syndrome - mutation testing
- R99 Common craniosynostosis syndromes or R100 Rare syndromic craniosynostosis or isolated multisuture synostosis should be used where features are atypical and a broader range of genes are likely to be causative

Referrals for testing will be triaged by the Genomic Laboratory; testing should be targeted at those where a genetic or genomic diagnosis will guide management for the proband or family.

Where in Pathway

At presentation

Requesting Specialties

- Clinical Genetics

Specialist Service Group

- Musculoskeletal

Associated Tests

Code	Name	Optional Family Structure	Scope(s)	Target Type	Target Name	Method
R23.1	FGFR2 c.755 and c.758 Targeted mutation testing	Singleton	Small variants	Single interval	FGFR2 c.755 and c.758	Targeted mutation testing

R416 Syndromic & non-syndromic craniosynostosis involving midline sutures

Testing Criteria

1. Patients presenting with confirmed craniosynostosis involving/including the metopic suture (trigonocephaly), OR
2. Sagittal suture, OR
3. both sagittal and metopic sutures.

Overlapping indications

- R100 Rare syndromic craniosynostosis or isolated multisuture synostosis

Where in Pathway

At presentation and following discussion with a consultant in clinical genetics or craniofacial neurosurgeon or another specialist approved by the GLH.

Requesting Specialties

- Clinical Genetics
- Neurosurgery

Specialist Service Group

- Musculoskeletal

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R416.1	Syndromic & non-syndromic craniosynostosis involving midline sutures	Singleton	Small variant detection	Single gene(s)	SMAD6 (1395)	Single gene sequencing < 10 amplicons

Gene Panels for Craniosynostosis (2)

R99 Common craniosynostosis syndromes

Testing Criteria

Recognisable multisuture craniosynostosis syndromes consistent with variants in EFNB1, ERF, FGFR1 common hot spots, FGFR2 common hot spots, FGFR3 common hot spots, TCF12 or TWIST1 or with unicoronal or bicoronal craniosynostosis

Overlapping indications

- R100 Rare syndromic craniosynostosis or isolated multisuture synostosis test should be used where features are not consistent with variants in EFNB1, ERF, FGFR1 common hot spots, FGFR2 common hot spots, FGFR3 common hot spots, TCF12 or TWIST1

Referrals for testing will be triaged by the Genomic Laboratory; testing should be targeted at those where a genetic or genomic diagnosis will guide management for the proband or family.

Where in Pathway

At presentation

Requesting Specialties

- Clinical Genetics

Specialist Service Group

- Musculoskeletal

Associated Tests

Please note all the tests below will be undertaken for R99 Clinical Indication requests, unless clinical presentation and/or initial results indicate all tests are not necessary

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R99.1	Common craniosynostosis syndromes Small panel	Singleton	Small variants	Panel of genes or loci	Common craniosynostosis syndromes (507)	Small panel
R99.2	Common craniosynostosis syndromes MLPA or equivalent	Singleton	Exon level CNVs	Panel of genes or loci	Common craniosynostosis syndromes (507)	MLPA or equivalent

R100 Rare syndromic craniosynostosis or isolated multisuture synostosis

Testing Criteria

Rare syndromic craniosynostosis syndrome or isolated multisuture synostosis, confirmed by skull scan where possible

Variants in EFNB1, ERF, FGFR1 common hot spots, FGFR2 common hot spots, FGFR3 common hot spots, TCF12 or TWIST1 must have been excluded on targeted genetic testing (R99 Common craniosynostosis syndromes)

Overlapping indications

- R99 Common craniosynostosis syndromes should be used where features are consistent with variants in EFNB1, ERF, FGFR1 common hot spots, FGFR2 common hot spots, FGFR3 common hot spots, TCF12 or TWIST1

Referrals for testing will be triaged by the Genomic Laboratory; testing should be targeted at those where a genetic or genomic diagnosis will guide management for the proband or family.

NOTE: If the SMO gene is suspected as causative, a tissue sample will be required for testing

Where in Pathway

At presentation

Requesting Specialties

- Clinical Genetics

Specialist Service Group

- Musculoskeletal

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R100.3	Craniosynostosis WGS (phase 1)	Trio or singleton	Exon level CNVs, Small variants	Panel of genes or loci	Craniosynostosis (168)	WGS

Current Status of PanelApp in R100 WGS

[PanelApp](#) [Panels](#) [Genes and Entities](#) [Activity](#) [Log in](#) [Register](#)

[Panels](#) / [Rare syndromic craniosynostosis or isolated multisuture synostosis](#)

The latest signed off version for the GMS is [v7.0](#). The current version, shown here, may differ from the signed-off version.

Rare syndromic craniosynostosis or isolated multisuture synostosis (Version 7.1)

Level 2: Musculoskeletal

Relevant disorders: Craniosynostosis syndromes, Craniosynostosis syndromes phenotypes, Rare syndromic craniosynostosis or isolated multisuture synostosis, Craniosynostosis, R100
Panel types: Rare Disease 100K, GMS Rare Disease Virtual, GMS signed-off
Latest signed off version: [v7.0](#) (12 Aug 2026)

[Download Latest Signed-Off Version](#)

199 Entities

199 reviewed, 83 green

List ↑	Entity	Reviews	Mode of inheritance	Details
Filter Entities		199 Entities		
Green	ACTB	2 reviews 2 green	MONOALLELIC, autosomal or pseudoautosomal, NOT imprinted	Sources - Expert list - Expert Review Green Phenotypes - Baraitser-Winter syndrome 1, OMIM:243310 - Baraitser-Winter syndrome 1, MONDO:0009470 Tags missense
Green	ACTG1	1 review 1 green	MONOALLELIC, autosomal or pseudoautosomal, imprinted status unknown	Sources - Expert Review Green - Literature

NIPD in Craniosynostosis (1)

R306 NIPD for Apert syndrome - variant testing

Testing Criteria

Pregnancy in which NIPD for Apert syndrome is required

Either:

1. Abnormal ultrasound findings suggestive of Apert syndrome with acrocephaly, proptosis AND symmetrical syndactyly, OR
2. At risk pregnancy due to paternal Apert syndrome

Referrals for testing will be triaged by the Genomic Laboratory; testing should be targeted at those where a genetic or genomic diagnosis will guide management for the proband or family.

Where in Pathway

Testing performed after 8 weeks in pregnancy as confirmed by dating scan

Requesting Specialties

- Clinical Genetics
- Fetal Medicine

Specialist Service Group

- Prenatal

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R306.1	FGFR2 NIPD – Apert	Singleton	Small variants	Single gene(s)	FGFR2	NIPD

NIPD in Craniosynostosis (2)

R307 NIPD for Crouzon syndrome with acanthosis nigricans - variant testing

Testing Criteria

Pregnancy in which NIPD for Crouzon syndrome with acanthosis nigricans is required due to paternal Crouzon syndrome with acanthosis nigricans and the variant is confirmed.

Referrals for testing will be triaged by the Genomic Laboratory; testing should be targeted at those where a genetic or genomic diagnosis will guide management for the proband or family.

Where in Pathway

Testing performed after 8 weeks in pregnancy as confirmed by dating scan

Requesting Specialties

- Clinical Genetics
- Fetal Medicine

Specialist Service Group

- Prenatal

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R307.1	FGFR3 NIPD – Crouzon	Singleton	Small variants	Single gene(s)	FGFR3	NIPD

NIPD in Craniosynostosis (3)

R308 NIPD for FGFR2-related craniosynostosis syndromes - variant testing

Testing Criteria

Pregnancy in which NIPD for FGFR2-related craniosynostosis is required due to paternal FGFR2-related craniosynostosis with causative variant confirmed.

Where in Pathway

Testing performed after 8 weeks in pregnancy as confirmed by dating scan

Requesting Specialties

- Clinical Genetics
- Fetal Medicine

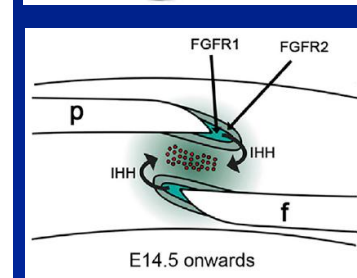
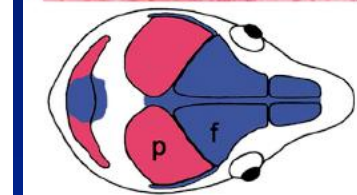
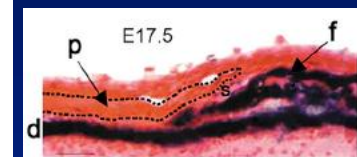
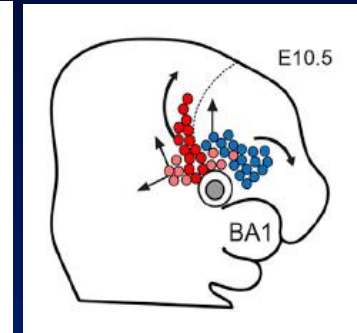
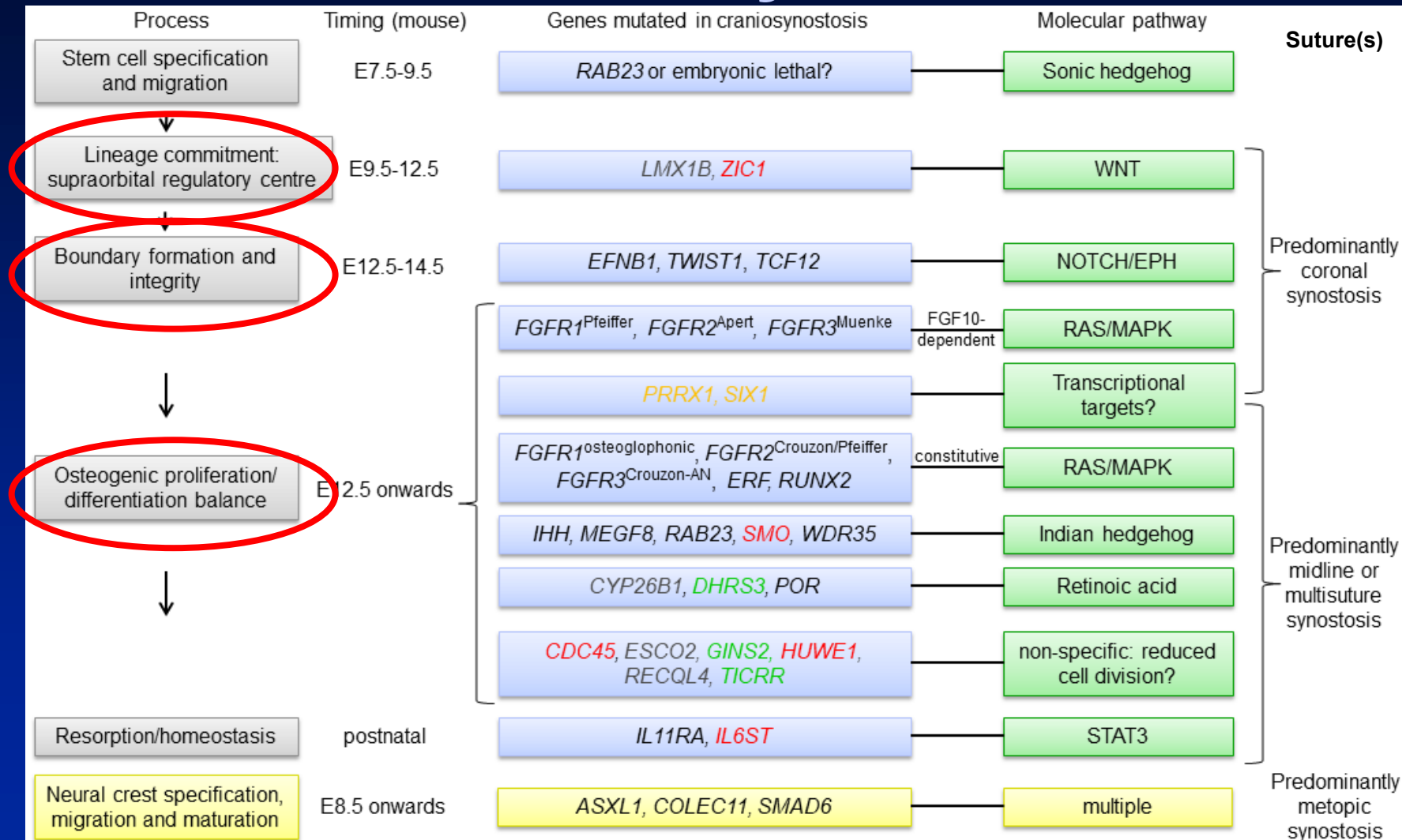
Specialist Service Group

- Prenatal

Associated Tests

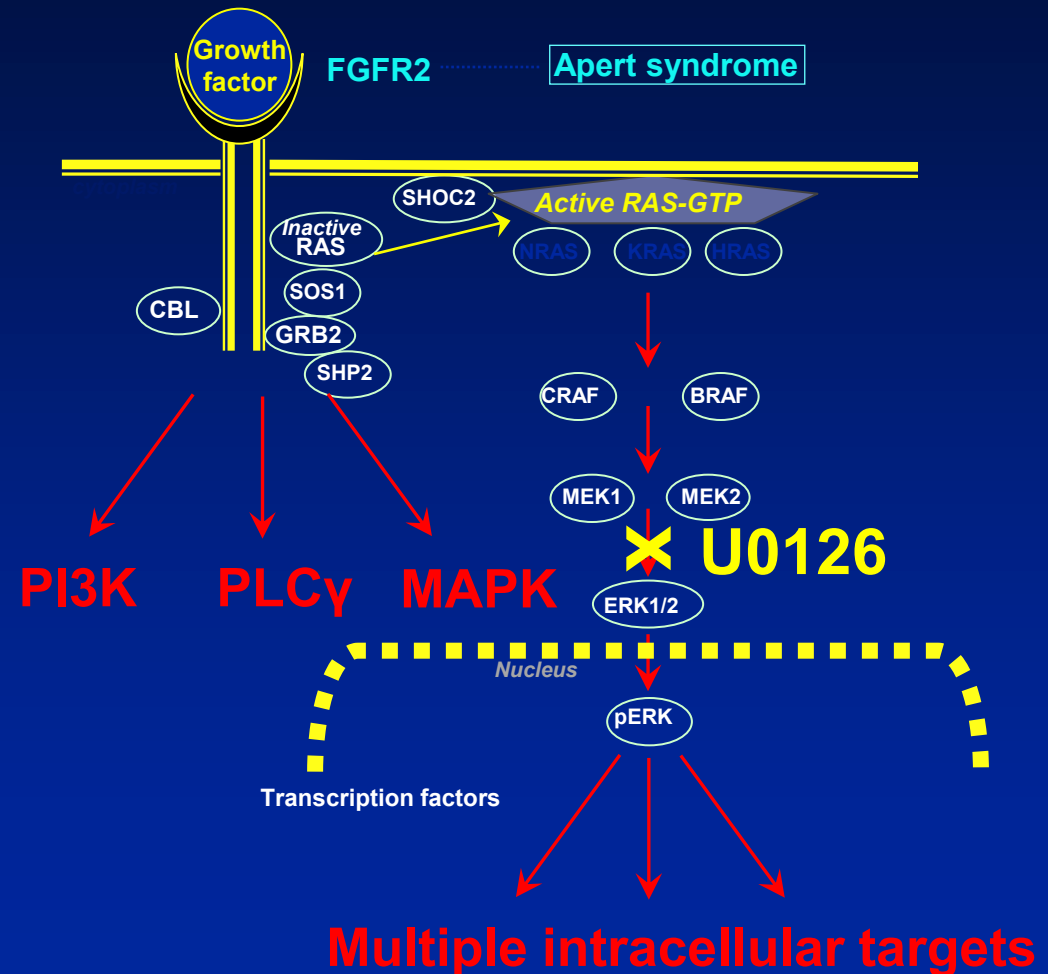
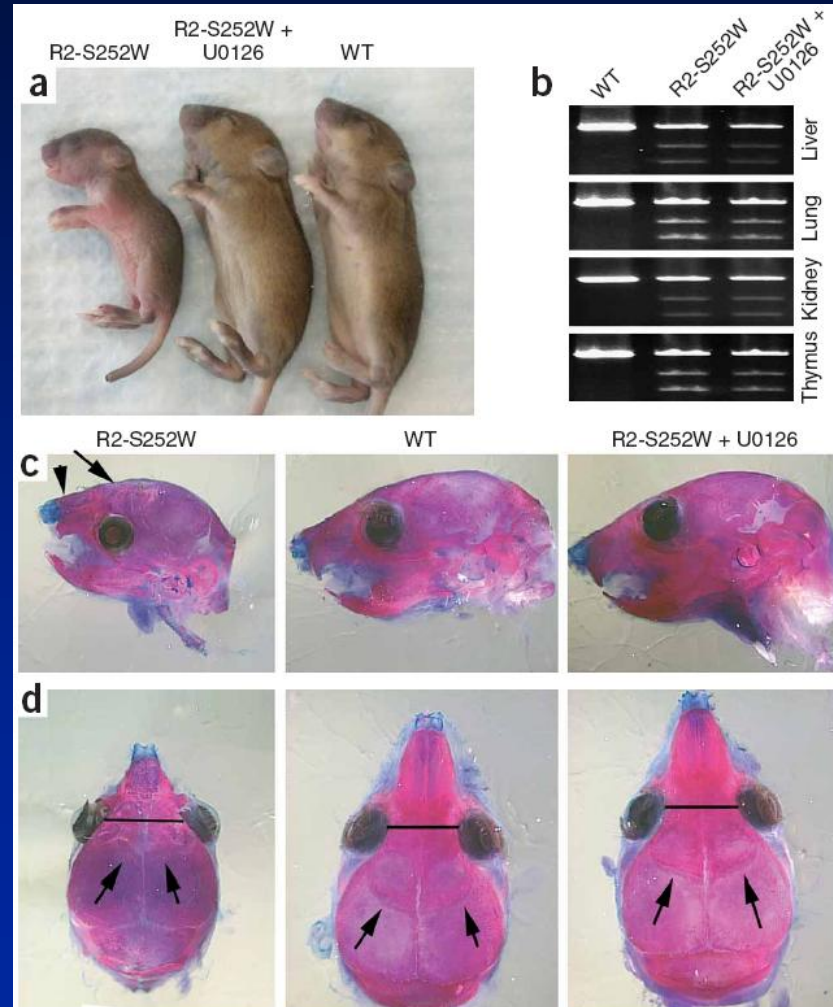
Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R308.1	FGFR2 NIPD - non-Apert FGFR2-related craniosynostosis	Singleton	Small variants	Single gene(s)	FGFR2	NIPD

A pathophysiological framework for craniosynostosis



Rescue of craniosynostosis in the Apert mouse by a MEK inhibitor

P8



Acknowledgements

Clinical Genetics Group, WIMM, Oxford



Isaac Walton, Rebecca Tooze, Steve Twigg, Dagmara Korona, Eduardo Calpena, Yang Pei



Akiko Hashimoto



Kerry Miller

Craniofacial Geneticists

Helen Brittain (Birmingham)

Daniela Pilz (Glasgow)

Debbie Shears (Oxford)

Astrid Weber, Siva Sithambaram (Liverpool)

Louise Wilson, Lara Menzies (Great Ormond Street)

