CRANIOSYNOSTOSIS SYNDROMES – HSS Service
Including Muenke (602849), Pfeiffer (101600), Crouzon (123500), Saethre-Chotzen (101400), Craniosynostosis 3 (615314), Craniosynostosis 4 (600775) and Craniosynostosis with dental anomalies (614188)

INTRODUCTION
The craniofacial service covers a diverse range of disorders characterised by craniosynostosis (premature fusion of one or more of the cranial sutures) resulting in facial deformity. Craniosynostosis has a prevalence of between 1/2100 and 1/3000 and is treated primarily by surgery. Severe cases cause complex distortions of the cranial anatomy and are associated with diverse complications, including raised intracranial pressure, hydrocephalus, cerebellar tonsillar herniation, deafness, visual problems, cleft palate, choanal atresia, dental malocclusion, respiratory problems, psychosocial difficulties, mental retardation and death. More than 100 syndromes have been identified which have craniosynostosis as a clinical feature, and up to 50 of these are monogenic. Mutation analysis enables refinement of the clinically defined classification, which is important for determination of recurrence risks, for prenatal testing, and to enable appropriate decisions regarding surgery to be made.

TESTING AND REFERRALS
All diagnostic samples should be accompanied by a completed clinical questionnaire & consent form (click here)
The aim is to provide a joint Molecular and Clinical service, and Professor Andrew Wilkie (+44 (0)1865 222619) is available for advice. We test:
- Clinically affected patients
- Relatives of clinically affected patients in whom a mutation has been identified
- Prenatal testing is available in cases where a mutation has been identified. This must be discussed with the laboratory & arranged in advance.

REFERRALS
From Clinical Genetics, Paediatrics, Craniofacial clinics, Dysmorphologists. Prenatal testing is only accepted from Clinical Genetics and / or Prenatal Diagnosis.

STRATEGY
Family: When a mutation has been identified in a family the individual is tested only for the familial mutation.
For new cases: 15-20% are due to dominant activating mutations in the paralogous FGFR1, FGFR2 or FGFR3 genes. A further ~5% of cases are due to inactivating mutations in the TWIST1 gene; ~1% are due to inactivating mutations in the ERF gene; and ~1% are due to inactivating mutations in the TCF12 gene. Different syndromes can be associated with mutations in the same FGFR gene (even the same mutation), whilst the same syndrome may be caused by mutations in different genes. A rare recessive form of craniosynostosis with associated dental anomalies (CRSDA) is due to mutations in the IL11RA gene.

The testing strategy reflects this diversity and the level of testing done depends on the individual’s clinical features. We offer 5 types of testing – a level 1 screen, a TCF12 gene screen, a level 2 screen, an ERF gene screen and dosage analysis by MLPA. The level 1 screen (together with dosage analysis, if appropriate) is done on all samples initially, with the other tests available as a reflex test dependant on the phenotype. IL11RA testing would be offered in patients with multi suture synostosis, tooth anomalies and/or consanguinity who have screened negative for mutations on a level 1, 2 and/or ERF screen.

TECHNICAL INFORMATION
Level 1 screen: Bidirectional sequencing analysis of FGFR3 exons 7 & 10, FGFR2 exons Illa (8) & IIlc (10), TWIST1 exon 1, & FGFR1 exon 7.
TCF12 screen: Bidirectional sequencing analysis of exons 2-20 and exon 8A of TCF12.
Level 2 screen: Bidirectional sequencing analysis of FGFR2 exons 3, 5, 11, 14, 15, 17 & 18.
ERF screen: Bidirectional sequencing analysis of exons 1-4 of ERF.
IL11RA screen: Bidirectional sequencing analysis of exons 2-13 of IL11RA.
MLPA: Dosage across all exons of the craniofacial genes TWIST1, ALX1, ALX3, MSX2, RUNX2 and EFNB1 and 3 exons of ALX4.

CLINICAL SENSITIVITY
Level 1 screen: This analysis detects 90-95% of craniosynostosis variants identified to date.
TCF12 screen: TCF12 variants were detected in 4/402 (1.0%) of all patients requiring surgery for craniosynostosis in the extended Oxford cohort (patients from 1998-2006). In individuals with coronal synostosis in whom no mutation of FGFR1, FGFR2, FGFR3 and TWIST1 has been identified, pick-up rate is ~17% (Sharma et al, 2013, Nat Genet, 45 (3): 304-7).
Level 2 screen: This screen covers all further exons in FGFR2 in which variants have been described.
ERF screen: Variants were detected in 5/402 (1.2%) of all patients requiring surgery for craniosynostosis in the extended Oxford cohort (patients from 1998-2006). In individuals with multi-suture synostosis, pick up rate was ~12% (Twigg et al, 2013, Nat Genet, 45(3): 308-13).
IL11RA screen: In cases with multi-suture synostosis, tooth anomalies and/or consanguinity and in whom no mutation has been identified on a level 1 screen the sensitivity is 10-20%. In subjects with multisuture synostosis alone with no variant detected on level 1 screen, the sensitivity is ~1%.
MLPA – Craniosynostosis has been reported in association with deletions and duplications of the TWIST1 gene.

TARGET REPORTING TIMES - Supraregionally funded by HSS for referrals from the UK.
Diagnostic: 8 weeks
Familial Mutation test: 10 days
Prenatal testing (includes maternal contamination check): 3 days

N.B. Details are correct for the date of printing only – last updated 11/06/2015