ANGELMAN SYNDROME (AS)
OMIM # 105830

INTRODUCTION
Angelman syndrome (AS) is a neuro-developmental disorder, affecting 1/15,000 to 1/20,000 individuals. It is characterised by severe motor and intellectual retardation, seizures associated with characteristic EEG traces, microcephaly, ataxia, frequent jerky movements and flapping of the arms and hands, hypotonia, hyperactivity, absence of speech, a characteristic face and a happy disposition. The AS phenotype results from the lack of a maternal contribution at 15q11-q13. This can be caused by a deletion (70-75%), paternal uniparental disomy or UPD (3-7%), microdeletions of the imprinting centre (10-15% of patients with an imprinting defect), or rarely an imprinting defect in the 15q region (~1%). These disease mechanisms can all be detected by studying methylation patterns within the 15q11-q13 region. In addition, approximately 20% have a normal methylation pattern and are believed to have a mutation in the putative Angelman gene, UBE3A.

Determining the disease mechanism is important as it enables recurrence risks to be given to the family.
- Deletions and UPD are usually de novo events; therefore the recurrence risk is low (unless there is a maternal chromosomal rearrangement predisposing to UPD15).
- The vast majority of imprinting defects are sporadic methylation defects; therefore the recurrence risk is low. 10-15% of imprinting defects are due to imprinting centre mutations (microdeletions) and these may be de novo (with a low recurrence risk) or inherited with a recurrence risk of up to 50%.
- UBE3A mutations can be de novo; with a low recurrence risk, or inherited with a recurrence risk of up to 50%.

TESTING
Diagnostic
- Clinically affected patients

Prenatal
- Available to couples at risk of having a child affected with AS

REFERRALS
- From Clinical Genetics, paediatrics and other relevant specialties, e.g. neurology
- Prenatal referrals are only accepted from Clinical Genetics and where possible, arranged in advance
- UBE3A referrals are only accepted from Clinical Genetics

STRATEGY AND TECHNICAL INFORMATION
- Methylation-sensitive multiplex ligation probe amplification (MS-MLPA) analysis
  - Determines copy number and methylation status within the PWS/AS critical region
  - Can distinguish between large deletions (copy number and methylation changes), microdeletions of the imprinting centre and UPD/ sporadic imprinting defects (methylation changes only) but cannot distinguish between UPD and imprinting defects
- Microsatellite analysis
  - Performed to distinguish between UPD and sporadic imprinting defects, in order to provide families with recurrence risks
  - Provides a second independent test for prenatal diagnosis
- UBE3A sequencing analysis – only performed if MS-MLPA negative and clinical diagnosis of AS is strongly indicated
- Cytogenetic analysis can identify deletions and parental chromosomal rearrangements
- Cytogenetic analysis requires a separate blood sample, in lithium heparin. Samples should be sent to the Cytogenetics Laboratory at the address below.

NB: Similar analysis is undertaken for Prader-Willi syndrome (PWS)

TARGET REPORTING TIMES
Diagnostic (not UBE3A sequencing): 10 days
Diagnostic (UBE3A sequencing screen): 8 weeks
Prenatal testing (includes maternal contamination check): 3 days

N.B Details are correct for the date of printing only – last updated 02/09/2015