GENETIC COUNSELLING AND PRENATAL ARRAY. 2/5/2013.

CLASSIFICATION OF VARIANTS WITH REGARD TO PATHOGENICITY.

*** pathogenic.**

- the CNV is known to be associated with a phenotype (e.g. del22q11.2, del15q11-13, del4p, etc) or
- the CNV results in a known effect on gene function and know phenotypic effect

*** benign variants without functional consequences.**

Repeatedly found in the normal population and not enriched in individuals with abnormal phenotypes.

***unclassified variants (UV) :** All other CNV's

In principle, unclassified variants are not communicated and parental analysis is not performed, unless when one expects that this will add to the interpretation of the U.V. and to the decision to communicate this CNV. Examples include CNV's with a higher degree of suspicion that they may cause a phenotype (size, number of genes, percentage of overlap with reported pathogenic CNV's, phenotype associated with the reported CNV, number of cases described, …), the presence of ultrasound anomalies, family history etc. When this UV is de novo (and after confirmation of paternity), it will be communicated.

ad hoc committee to deal with uncertain situations.

In case of uncertainty, we will to try and reach a consensus, ad hoc, by consulting the ad hoc committee (see below). This is done before the final protocol is issued.

INCIDENTAL FINDINGS.

Only highly penetrant monogenic disorders are considered, with validated evidence on the phenotype associated with the deletion or duplication. Three categories are distinguished, even though not ideal.

-**Late-onset genetic disorders with clinical utility :** CNV's causing late onset disorders, typically cancer caused by the deletion of a tumor suppressor gene, will be communicated if undeniable health benefit can be expected for the patient (fetus or parent). (see guidelines from the ACMG (2013)).

-Late onset disease without therapeutic possibilities: the responsible clinician takes the decision after consulting the ad hoc committee. If no consensus can be reached, the responsible clinician decides and communicates his decision to the ad hoc committee.

-Carrier for X-linked recessive disorders : will be communicated, both de novo or inherited.

-**Carrier for autosomal recessive disorders**, will not be communicated, unless the disorder is frequent (carrier frequency >1/50 and testing is available in Belgium: CFTR, SMA and Connexin 26).

SUSCEPTIBILITY CNV'S.

CNV's that are risk factors for developmental disorders will, in principle, not be communicated, unless the risk is sufficiently large and/or the CNV is associated with structural malformations for which ultrasound follow-up is indicated. Seven such frequent CNV's will be communicated:

-	Distal deletion 16p11.2	(SH2B1)	OMIM 613444
-	Deletion 16p11.2	(TBX6)	OMIM 611913
-	Distal deletion 1q21.1	(GJA5)	OMIM 612474
-	Deletion 17q12 = RCAD	(TCF2)	OMIM 614527
-	Distal duplication 1q21.1	(GJA5)	OMIM612475
-	Duplication 22q11.2	(TBX1)	OMIM 608363
-	Proximal deletion 1q21.1 / TAR	(HFE2)	OMIM 274000

Communicating other susceptibility CNV's may be appropriate when this is expected to influence the management of pregnancy by parents or physicians (e.g. family history, ultrasound anomalies).

INFORMED CONSENT

Providing pretest information on the different test results is strongly recommended, and is summarized in an information leaflet. The parents are not given an option to choose which information they wish to be returned. In case of an abnormal result (irrespective of which type), the parents should be offered extensive genetic counseling, without unnecessary delay.