REFERENCE LABORATORY GENETICS

ENAC ENSAYOS Nº 1065/LE2112

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MOLECULAR STUDY REPORT

Comparative genomic hybridization by array 60K (aCGH)

Case nº		Customer code	
Pacient name		Customer	
Date of birth	-	Patient reference	
Sample	☑ Amniotic fluid ☐ DNA from lymphoblastoid cell line ☐ Blood ☐ POC	Clinical service	
Reason for referral	Abnormal ultrasound findings. Mother has a balanced t(4;11)(p15;p15)		

Analysis code		Extraction date	
Reception date		Result date	

FORMULA:

arr[GRCh37] 4p16.3p15.2(72447_22526538)x1	**Pathogenic**
arr[GRCh37] 11p15.5p15.4(196966_6628701)x3	**Pathogenic**

RESULT AND INTERPRETATION:

- **arr[GRCh37] 4p16.3p15.2(72447_22526538)x1**. Terminal deletion of about ~22,4Mb on the short arm of chromosome 4, affecting the 4p16.3p15.2 region of the genome (fig. 1), which alters the structure and/or multiple doses of diferent RefSeq genes. This region is directly related to the Wolf-Hirschhorn syndrome with OMIM number: #194190.
- **arr[GRCh37] 11p15.5p15.4(196966_6628701)x3**. Terminal gain of about ~6,4Mb on the short arm of chromosome 11, affecting the 11p15.5p15.4 region of the genome (fig. 2), which alters the structure and/or multiple doses of diferent RefSeq genes. This region is directly related to two 11p15 microduplication syndromes, the Silver-Russell syndrome (OMIM: #180860), and the Beckwith-Wiedemann syndrome (OMIM: #130650).
- In the literature review carried out, there are very few works related to these two anomalies together, but yes of each of them in isolation. (literature review).
- These alterations are compatible with the unbalanced inheritance of t(4;11) of maternal origin. The derivative chromosome is inherited from the balanced translocation of the mother (information provided by the reference laboratory).
- Normal dose in sexual chromosomes corresponding to a male sample.

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CONCLUSIONS:

- The analysis of the sample with the array CGH, reveals copy number alterations which may involve alterations that cause disease. These alterations are the causes of clinical findings, so they are pathogenic.
- We have identified a terminal deletion of ~22,4Mb on the short arm of chromosome 4, affecting the 4p16.3p15.2 region of the genome. This anomaly does not overlap with polymorphic CNVs described in the general population. The detected variant is pathogenic and related to Wolf-Hirschhorn syndrome (GeneReviews, Decipher, Orphanet).

- We have identified a terminal amplification of ~6,4Mb on the short arm of chromosome 11, affecting the 11p15.5p15.4 region of the genome. This anomaly does not overlap with polymorphic CNVs described in the general population. The detected variant is pathogenic and related to SRS or BWS. (Orphanet SRS / Orphanet BWS, Genereviews).

- We have reviewed the different databases like DECIPHER, ISCA and ECARUCA to find patients with similar aberrations to the case in question, and there are different patients described in them with different clinical manifestations.

- We have reviewed the clinical implication of these aberrations:

  - del(4)(pter)

  Wolf-Hischhorn syndrome is caused by the partial deletion of the short arms of chromosome 4. Critical región admitted is 4p16.3 (WHS). The major features of this disorder include a characteristic facial appearance: broad, flat nasal brigde and a high forehead, described as a “Greek warrior helmet”, short philtrum, micrognathia and ears pits o tags. Other major features are delayed growth and develoment, intellectual disability (ranges from mild to severe) seizures and hypotonia. Additional features include skelethal abnormalities (scoliosis and kyphosis), cleft lip/palate and abnormalities of the eyes, heart, genitourinary tract and brain. Socialization skills are strong, while verbal communication and language skills tend to be weaker.

  - dup(11)(qter)

  11p15.5p15.4 amplification is related to two entities with different clinical: Silver-Russell syndrome (RSS) and Beckwith-Wiedemann (BWS).

  Silver-Russell syndrome, congenital condition, is associated with dwarfism with poor growth before and after birth. It is characterized by stunted growth and limb or facial asymmetry. Symptoms range over a broad clinical spectrum from severe to so mild that they go undetected. Other features may include poor appetite, clinodactyly (curved finger), digestive system abnormalities, delayed development, and/or learning disabilities.

  Most cases are sporadic. In rare cases, RSS may be inherited in an autosomal dominant, autosomal recessive and linked X manner.

  Wiedemann-Beckwith syndrome is classified as an overgrowth syndrome. Symptoms: asymmetric growth (hemihyperplasia), omphalocele or other abdominal wall defect at birth. Hypoglycemia in infancy, an abnormally large tongue (macroglossia), abnormally large abdominal organs, creases or pits in the skin near the ears, and kidney abnormalities. Affected children have an increased risk to develop tumors. The most frequent are Wilms tumor, hepatoblastoma and rhabdomyosarcoma. The etiology is complex because several genes are involved, some of which are subject to genetic imprinting. Diagnosis of BWS is based on symptoms with the support of genetic testing.

  Clinical findings are consistent with the clinical features.

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- When a patient presents two subtelomeric rearrangements, it is difficult to characterize the phenotype, since the expression of both aberrations can not be known.
- These alterations are inherited in an unbalanced way due to the t(4;11) of maternal origin (information provided by the reference laboratory).
- Prenatal cytogenetic study or CGHarray study it is indicated.
- Genetic counseling is strongly recommended.

Signed: Carles Garrido
Head of Department

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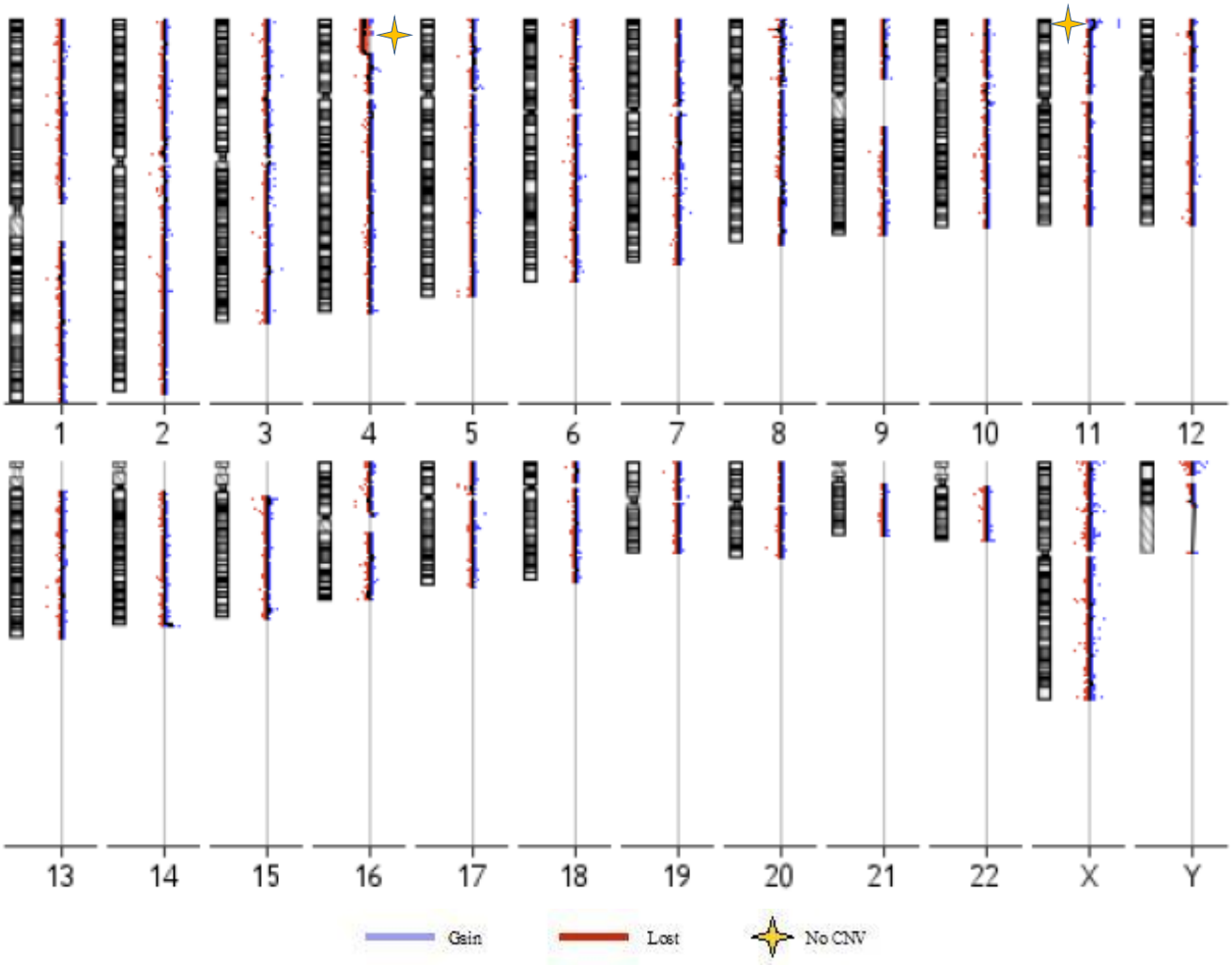
GENOME VIEW:



Molecular karyotyping using ISCA array CGH 60K. Gains in blue to the right of the ideogram and losses to the left in the red color.

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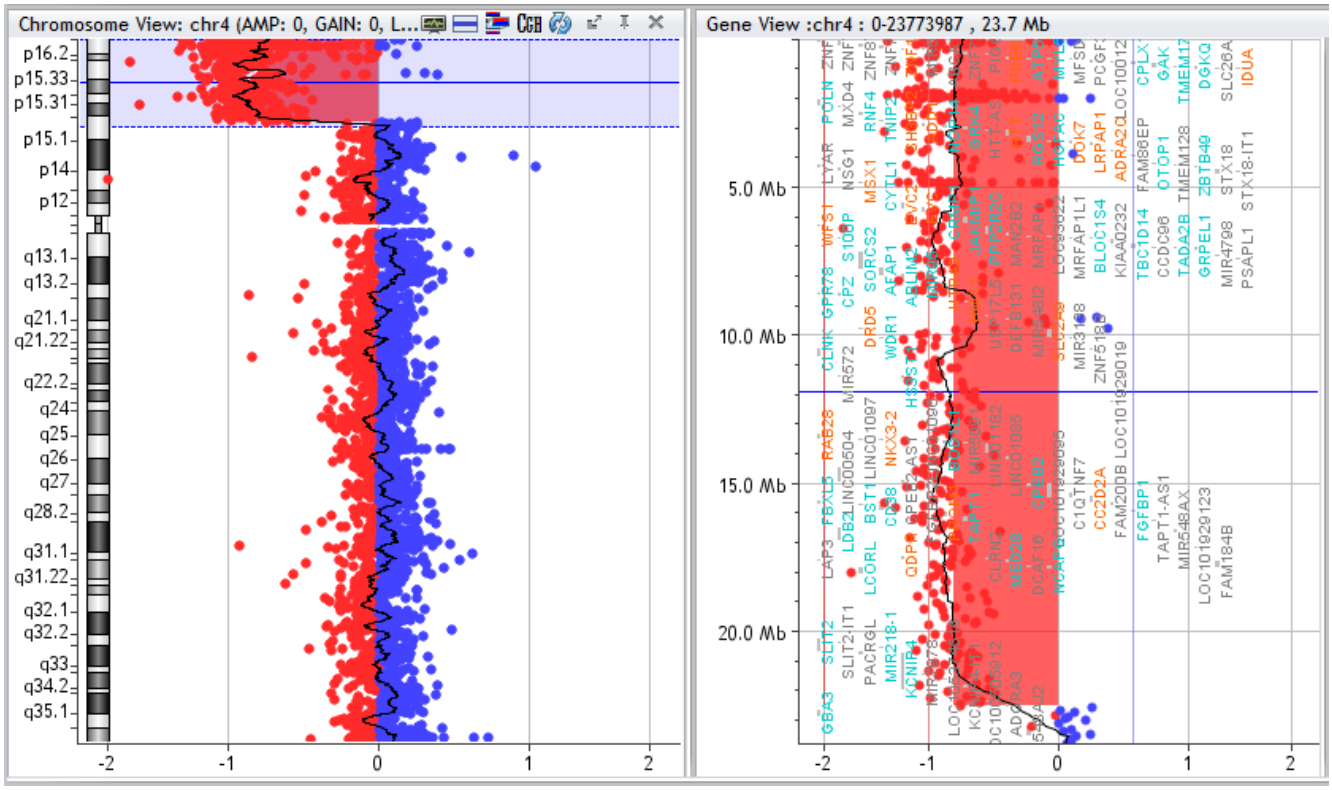
CHROMOSOME 4

Figure 1: Detail of molecular karyotype where you can appreciate the terminal ~ 22,4Mb deletion of the short arm of chromosome 4.



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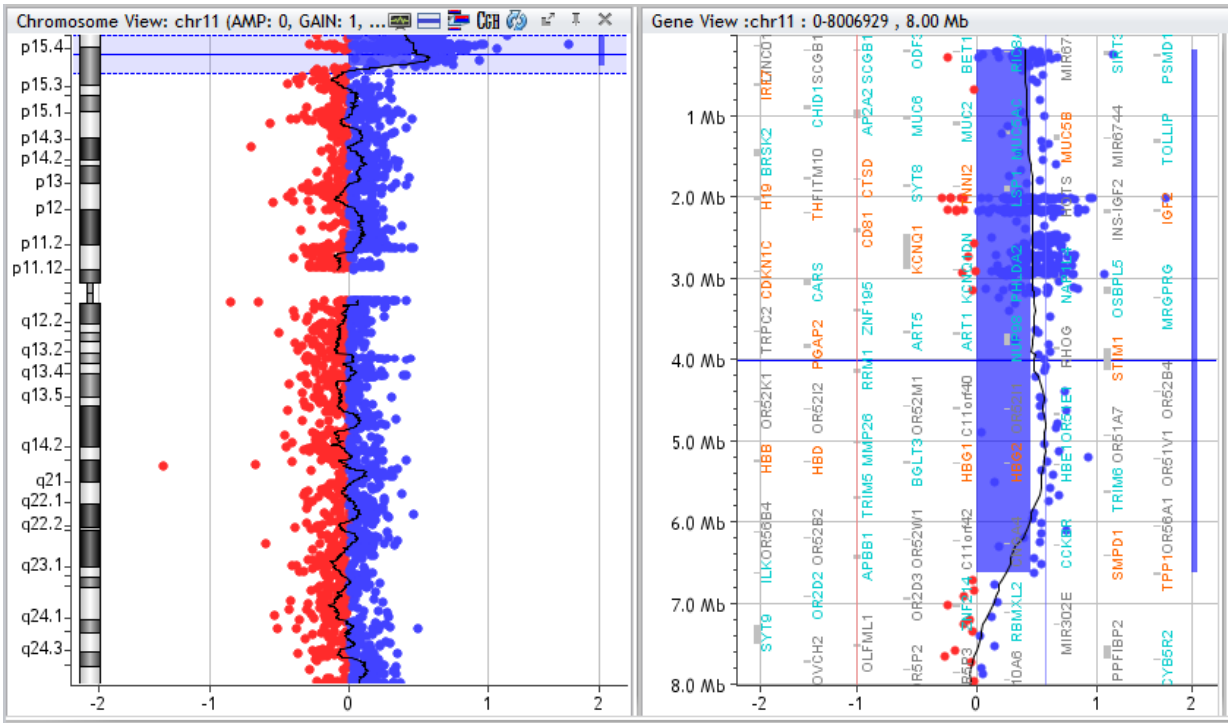
CHROMOSOME 11

Figure 2: Detail of molecular karyotype where you can appreciate the terminal ~ 6,4Mb amplification of the long arm of chromosome 11.



METHODS SECTION:

✓ Hybridization responsible :	AMM
✓ Hybridization date :	15/05/19
✓ Type of chip:	ISCA V2 arrayCGH 60K
✓ Hybridization control:	Agilent euro male
✓ Hybridization type:	Direct labeling
✓ Hybridization quality (Agilent's DLRS):	0.114
✓ Analysis software:	Cytogenomics
✓ Detection parameters alterations:	Algorithm ADM2_6;0;abs(log2ratio)_0;25;probes_3
✓ Reference assembly:	GRCh37
✓ Platform:	Agilent
✓ Responsible for validation:	CGF

TECHNICAL LIMITATIONS:

The oligonucleotide microarray comparative genomic hybridization (CGH) allows to detect duplications and deletions of target genomic regions interrogated by the probes that make up the chip. It use microarray probes

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which interrogate pericentromeric regions, subtelomeric rearrangements and recurrent euchromatic regions, located on all chromosomes, at an approximate density of 1 probe every 35 Kb, these are the parameters used for detecting an standard resolution between 100 - 125 Kb . Out of the candidate regions, the average coverage is 1 probe every 125 Kb, which can detect changes > 350Kb . We recall that by aCGH can not be detected balanced rearrangements (reciprocal translocations, Robertsonian translocations, inversions and/or unbalanced inserts), small ins/dels, point mutations, copy number alterations in less of 40%, or alteration of number of copy outside the regions interrogated by the probes that make up the chip. In addition, the oligonucleotide probes used in this microarray are not designed to detect uniparental disomy or alterations in methylation.

Polyploidy detection: the array-CGH can not detect some triploidies, such as 69, XXX, and tetraploidies as 92, XXXX or 92, XXYY, but can detect abnormalities of sex chromosomes as XXY, XYYY or XXXY. This result may reveal the existence of Klinefelter syndrome and its variants or correspond to a triploidy or tetraploidy that are technically not detectable.

REPORT CRITERIA:

The identified variants were compared with those recorded in the Database of Genomic Variants (last updated July 2, 2013). These variants have been classified as pathogenic, VOUS (Variants of unknown significance, variants of uncertain clinical significance) and / or benign, as recommended by the American College of Medical Genetics standards and guidelines for interpretation and reporting of postnatal constitutional copy number variants [1, 2, 3]. This report format is based on that proposed by the Consensus Group for the implementation of Arrays [CGH and SNP-arrays] in clinical genetics [4]. Genomic formula as current ISCN nomenclature [5]. As a general rule, variants of uncertain significance (and/or susceptibility without clear phenotypic effect (according to current knowledge) are not reported , unless by express desire stated in the application.

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The clinical relevance of chromosomal and variants of normal anomalies is interpreted using the information available at present and could change in the future. are not informed state carrier of recessive characters, interpreted as benign CNVs (Genet Med 2011; 13: 680-85) and variants of uncertain significance under 400Kb (Am J Hum Genet 2010; 86: 749-764), unless deemed clinically relevant. As a general rule, no variants of uncertain significance will be reported (and/or susceptibility no clear phenotypic effect), according to current knowledge, unless express wish stated in the application. Keep in mind that the study of variants number of polymorphic copy and/or causing disease is an active field of research in medical genetics, so that it is possible that the array used altered copy number were detected of uncertain meaning, and that the clinical relevance of the identified variants is subject to review in the future. A normal result of this genetic test does not exclude the possibility that the clinical phenotype may be due to genetic causes not tested with this microarray. As with any genetic test , there is a very small chance (<5 %) that an erroneous result is issued. In case the results obtained and reported here are not consistent with the clinical diagnosis made or family history, please contact us to discuss the case for, if necessary, schedule new tests.

DISCLAIMER CLAUSE:

Studies and DNA microarray analysis performed by our lab are intended solely for qualified professionals for health interpretation. The results obtained by these studies do not in themselves constitute medical advice, diagnosis or treatment, and should be so interpreted. Only a trained professional can properly interpret studies and DNA microarray analysis and provide a diagnosis or to prescribe to a patient based on these results a treatment. Consequently, no information obtained from our studies and analyzes can be used to replace the advice and diagnosis of a qualified professional. The lab is not responsible for your use of the contracting their services and products on the results obtained through its analyzes and studies, nor of any harmful consequences of such use, expressly reserving exercise appropriate legal action in the event from improper use of the above studies and analysis.

The contracting of the studies and analysis referred to above, made by our lab, you may not modify, reduce, extend or alter in any way the content of this report. Therefore, the contractor waives irrevocably the lab any liability or any adverse consequences resulting directly or indirectly from the breach of this obligation.

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