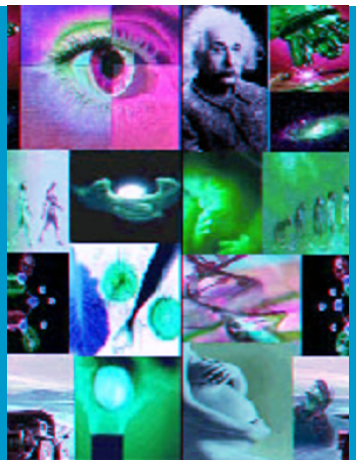
Comisión Nacional de Investigación Científica y Tecnológica - CONICYT



PROGRAMA FONDECYT

INFORME FINAL

ETAPA 2016

COMISIÓN NACIONAL DE INVESTIGACION CIENTÍFICA Y TECNOLÓGICA

VERSION OFICIAL NÂº 2

FECHA: 14/03/2017

Nº PROYECTO : 1130392 **DURACIÓN :** 4 años **AÑO ETAPA :** 2016

TÍTULO PROYECTO : GENETIC MODIFIERS OF THE CARDIOVASCULAR PHENOTYPE OF CHROMOSOME 22Q11 MICRODELETION SYNDROME: NEXT-GENERATION SEQUENCING OF CANDIDATE REGIONS IDENTIFIED BY GENOME-WIDE ASSOCIATION ANALYSIS

DISCIPLINA PRINCIPAL : G2 CARDIOLOGIA, FISIOLOGIA CARDIOVASCULA

GRUPO DE ESTUDIO : MEDICINA G2-G3

INVESTIGADOR(A) RESPONSABLE : MARIA GABRIELA REPETTO LISBOA

DIRECCIÓN :

COMUNA :

CIUDAD : Santiago

REGIÓN : METROPOLITANA

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INFORME FINAL
PROYECTO FONDECYT REGULAR

MODIFICACIONES ACADÉMICAS

Modificaciones Académicas Aprobadas

Nº	Solicitudes Aprobadas	Ingresado el	Ingresado por
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2	ANNEX_1._abstract_for_Weinstein_Meeting_2015.pdf	09/03/2015 15:19	MREPETTO
Ver documento adjunto: https://servicios.conicyt.cl/sial/index.php/investigador/f2_modificaciones_academicas/forzar_descarga_adjunto_pdf/1130392/2014/1/49/			
3	Solicitud_de_cambio_de_metodologia_2014.pdf	09/03/2015 15:16	MREPETTO
Ver documento adjunto: https://servicios.conicyt.cl/sial/index.php/investigador/f2_modificaciones_academicas/forzar_descarga_adjunto_pdf/1130392/2014/1/48/			

Nuevas Solicitudes para Evaluación

Nº	Solicitudes para Evaluación
El informe no presenta solicitudes.	

Otros Aspectos Importantes a Considerar
Sin comentarios.

PROJECT RESULTS:

Introduction

Chromosome 22q11.2 microdeletion syndrome (22q11DS) is a relatively common but largely underdiagnosed genetic condition, with an estimated frequency of 1/4000 live births. It is caused by the loss of approximately 3Mb or 60 genes in chr22:18,800,000-21,400,000 (hg19). The clinical manifestations include (i) congenital anomalies, such as congenital heart disease (CHD), palate anomalies (PA), endocrine deficiencies, among others, and (ii) neuropsychiatric manifestations, such as developmental delay, intellectual disabilities and high risk of psychosis with a 25% lifetime risk of schizophrenia. Most patients share the same deletion size and location, but the clinical manifestations vary widely; this phenotypic heterogeneity probably contributes to the marked underdiagnosis. Based on published incidence figures and known cases from Chile, we have estimated that less than 20% of expected cases have been clinically confirmed.

The identification of the underlying genetic causes of the clinical variation in CHD frequency is the main aim of our line of research. We explored a limited number of candidate genes in Fondecyt #1061051, common variants in a genome-wide association study (GWAS) in grant #1100131 and rare variants in this project. Selected result from these previous grants were used to enrich the current analysis.

Objectives and Methods

Approximately 50-60% of patients have CHD, the reason for the incomplete penetrance of this severe manifestation is unknown, and we hypothesized that there may be a role for modifier genes elsewhere in the genome. The main objective of this proposal was "To identify potential genes involved in the presence of CHD through whole exome sequence (WES) in patients with 22q11 deletion" (objective modified in 2014). This was designed as a case-control study, to include patients with molecularly proven 22q11DS: cases with conotruncal heart anomalies and controls with normal cardiac anatomy.

Results

Objective 1: To characterize, in detail, the clinical manifestations of at least 150 patients with 22q11.2 microdeletion, with emphasis on cardiac and great vessel anatomy, and the association of cardiovascular anomalies with other features of the syndrome. To date, 281 individuals with 22q11 deletion have participated in our ongoing studies. Of these, 66 are new patients, consented during this grant. Females account for 54.1% of the group. Current median age is 15.7 years; ranging from 1-55 years. At least 17 individuals (6.8%) are known to have an inherited deletion, but this is probably an underestimate since few parents have had molecular testing. Regarding perinatal history, 32% were small for gestational age infants, higher than the general population frequency of 10%.

CHD was present in 51% of patients. The most common were ventricular septal defects (VSD) in 46.8% among those with CHD, followed by tetralogy of Fallot (TOF) in 37.4%. Other conotruncal outflow tract CHDs and their relative frequencies were interrupted aortic arch (IAA) in 12%, truncus arteriosus (TA) in 6.4% and double outlet right ventricle (DORV) in 3.5%. Palate anomalies were seen in 65.5% of patients, with submucous cleft palate present in 42.5%. Relevant associations with CHD found in the cohort included

-case fatality rate (CFR) (OR 5.27, CI 95% 2.06-13.99). CFR for each defect was, on average, 3.65 higher in patients with 22q11DS than in the general Chilean population with "non-syndromic" CHD, implying that this is a very high risk group (published in Repetto et al, BMJ Open 2014)[1]

-low birth weight (OR 1.89, CI 1.04-3.45) (Repetto et al, presented at Congreso de la Sociedad de Genética de Chile 2015).

-scoliosis (p 0.04) this may be a primary phenomenon of the syndrome, or secondary to thoracotomy during cardiac surgery.

No significant associations were identified between CHD and gender, palate anomalies and other clinical features/congenital anomalies

Student participation: Francisco Navarro, Medical Student at Universidad del Desarrollo, participated in statistical analysis of phenotypic data during 2016. An overview of clinical associations of CHD in 22q11DS has been accepted for presentation at the 7th World Congress of Pediatric Cardiology and Cardiovascular Surgery.

[1] this article has been cited in high impact journals, such as Lancet and Nature Reviews Disease Primers, among others

Of note, since we follow this cohort of patients for over a decade, we observed the development of movement disorder (Parkinsonism) in one of the adults with schizophrenia, with paradoxically increased striatal dopamine signaling in brain PET-CT (contrary to the decreased signaling seen in Parkinson´s disease. Similar findings were observed by our collaborators at the University of Toronto, suggesting the presence of high risk for development of neurodegeneration, movement disorders and dopamine dysregulation, a hypothesis that will be explored in our next FONDECYT project, and lead to a publication recently accepted in Brain (Butcher N et al, 2017).

Objective 2 "To identify potential genes involved in the presence of CHD through whole exome sequence (WES) in these patients". For this objective, we performed WES in samples from 68 patients with and without severe conotruncal heart defects. Eight were sequenced in our laboratory, and due to cost constraints, 60 were sequenced in the Northwest Genomics Center in the US. To enrich the data and analysis, we integrated results from our previous whole genome SNP (common variant) genotyping in 210 individuals and from our international collaborators.

2.1 Deletion size:

The 22q11.2 region contains several low copy repeats (LCRs), labelled A to D. This structure predisposes to rearrangements. There are 3 common deletion sizes: (i) a large 3Mb deletion, from LCRs A to D and involving approximately 60 genes, and 2 smaller deletions involving less genes: (ii) 2Mb, from LCRs A to C and (iii) 1.5 Mb, from LCRs A to B. The large A-D deletion is present in > 90% of patients. We hypothesized that CHD modifier genes could be present within the deletion region and thus, we evaluated association between the presence of CHD or PA and deletion size, through literature review and metaanalysis of available pertinent data. Deletion sizes were assessed by array o by Multiple Ligation Probe Assay (MLPA). In our cohort, 93% of patients had the large A-D deletion, 2% had A-C deletion and 5% had the small A-B deletion. We found no evidence of association between deletion size and the presence of CHD (OR 1.22 (95th CI 0.78-1-92), suggesting that the main causative genes are within the common A-B segment (Figure 1) and that the presence of modifiers gene of the cardiac phenotype within the B-D segment is unlikely.

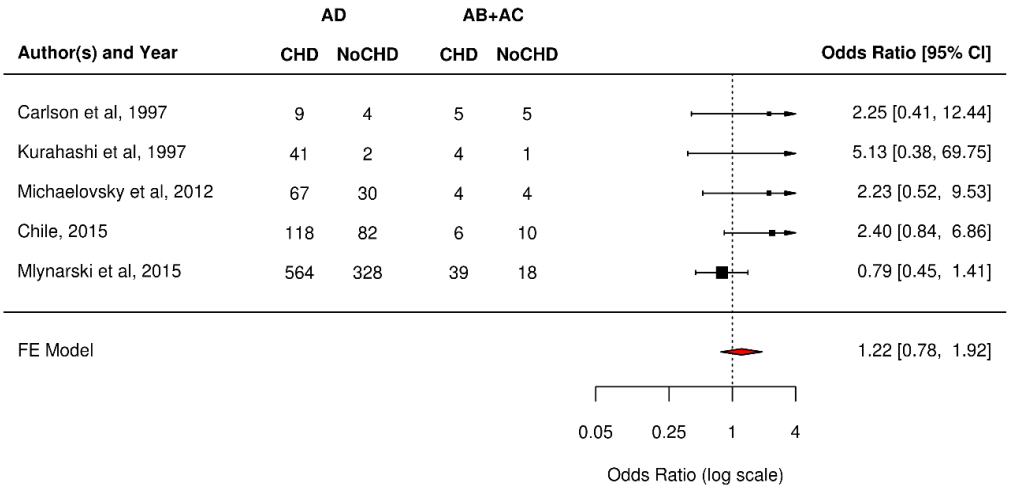

Figure 1. Forest plot of metaanalysis of association between deletion size and presence of CHD comparing individuals with large (A-D) vs non-large (A-C and A-B) deletions, using a fixed effects (FE) model (manuscript in preparation)

Student participation. Fernanda Rozas, MD, PhD(c) did a Research Unit of her PhD program in genomic analysis of 22q11 deletion, contributed to the metaanalysis and is first author on the manuscript currently in preparation.

2.2 Common variation

2.2.1 Single nucleotide variants (SNVs) This work was performed in collaboration with Bernice Morrow, PhD at Albert Einstein College of Medicine in New York, international collaborator in this grant. In an effort to increase sample size, given the stringent significance criteria required for genome wide studies, we pooled array and clinical data from the > 200 patients analyzed in our center with > 1000 individuals from different countries, mostly from North America and Europe. In a GWAS using Affymetrix v6.0 SNP arrays of a subgroup of 328 TOF cases versus 569 controls, all with 22q11.2DS, we identified 3 SNVs mapping to intron 61 of GPR98 gene (G Protein-Coupled Receptor 98) that were significantly associated with TOF. Genotyped SNP rs12519770 (p =3.19×

10−8; OR 1.69, 95% CI 1.39-2.06), as well as two imputed SNPs in this gene, rs7720206 (p = 2.22× 10−8) and chr5:90067043 (p = 2.10 × 10−8), showed the strongest association. GPR98 is located in chromosome region 5q14.3. (Figure 2A).

GPR98 encodes a large cell surface G protein-coupled receptor. Recessive mutations in this gene are responsible for Usher syndrome type II, a cause of hearing loss. It is weakly expressed in the developing heart, but is expressed in the neural tube and in neural crest cells, which later migrate to the conotruncal outflow tract. Functional studies will be relevant to assess its role in cardiac development and in the phenotype of the deletion. Another possibility is that the region contains regulatory sequences for other genes. Most GWAS loci affect regulation of genes nearby or at a distance, not necessarily the locus closest to the signal. Based upon this possibility, existing Hi-C chromatin conformation was analyzed by Dr Morrow´s group to identify genes that might be under shared transcriptional regulation within the region on 5q14.3. There are six genes in the topologically associated domain with GPR98 (Figure 2B). Among them, is the MEF2C gene (Myocyte-specific enhancer factor 2C), the closest one that is known to affect heart development in mammals and might be of interest for functional studies in the future.

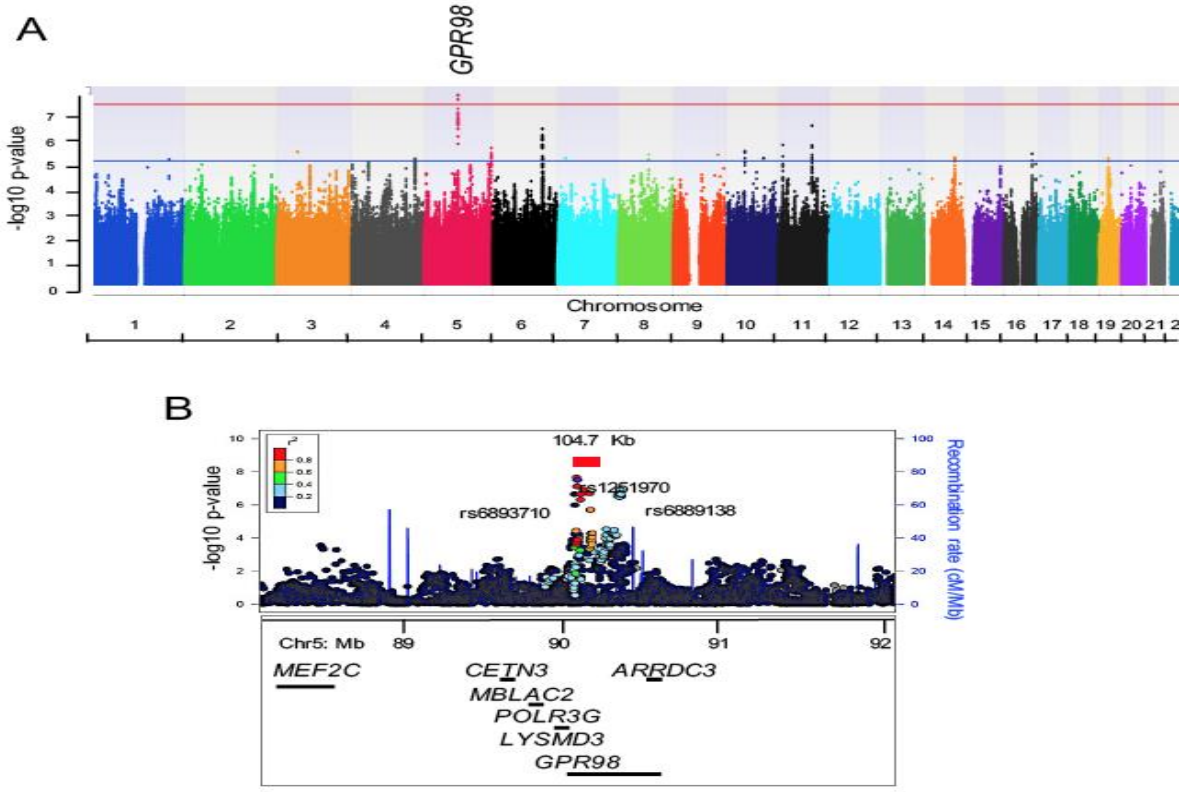

Figure 2: Genome wide association results for TOF in 22q11.2DS. (A) p-values in the Manhattan plot for TOF versus controls were plotted against their respective positions on the autosomal chromosomes for each SNP. The red line represents the genome-wide significance threshold (p-value = 5 × 10−8). The blue line represents the threshold for suggestive association (p-value = 1 × 10−5). A single locus (rs12519770) marked by the GPR98 gene reached genome wide significance. (B) LocusZoom plot of region of association at rs12519770 on 5q14.3 indicating −log10 p-values (y-axis) against the chromosomal positions of SNPs (x-axis). The genotyped SNP with the strongest association signal in each locus is represented as a purple diamond; the other SNPs are colored according to the extent of Linkage Disequilibrium (LD) with this SNP. Genes are indicated below the LocusZoom plot (Figure from Guo, Repetto, et al, submitted).

The findings were presented at the 66th Annual Meeting of the American Society of Human Genetics and a manuscript is currently under review at Circulation: Cardiovascular Genetics

2.2.2. Copy number variants (CNVs)

Affymetrix v6.0 SNP array results were evaluated for association of CHD with CNVs outside of the 22q11 region. In 214 samples from unrelated Chilean subjects with 22q11.2DS (105 cases with CHD and 109 controls without CHD), we found:

a) No difference in CNV burden (number or size of CNVs) between cases and controls

b) A statistically significant association between the presence of CHD and a partial duplication of KANSL1, involving exons 1 and 2 (p-value = 0.023, OR = 2.75, 95% CI = 1.17-7.03). This gene is located in region 17q21.31 and encodes for the KAT8 regulatory NSL complex, subunit 1, a nuclear protein that plays a role in chromatin modification. Variation in genes involved in epigenetic processes has been shown to be associated with non-syndromic CHD (Zaidi et al Nature 2013), and thus may be potentially relevant candidates for syndromic CHD as well. Bioinformatic analysis showed that KANSL1 and CRKL, a gene in the commonly deleted region at 22q11.2DS, are part of the same regulatory module in a miRNA-mRNA network (Figure 3). In summary, these results show that a KANSL1 microduplication, in combination with the 22q11.2 deletion, is associated with increased risk of CHD in these patients, suggesting that KANSL1 plays a role as a modifier gene in 22q11.2DS patients. A manuscript is currently under review at Scientific Reports.

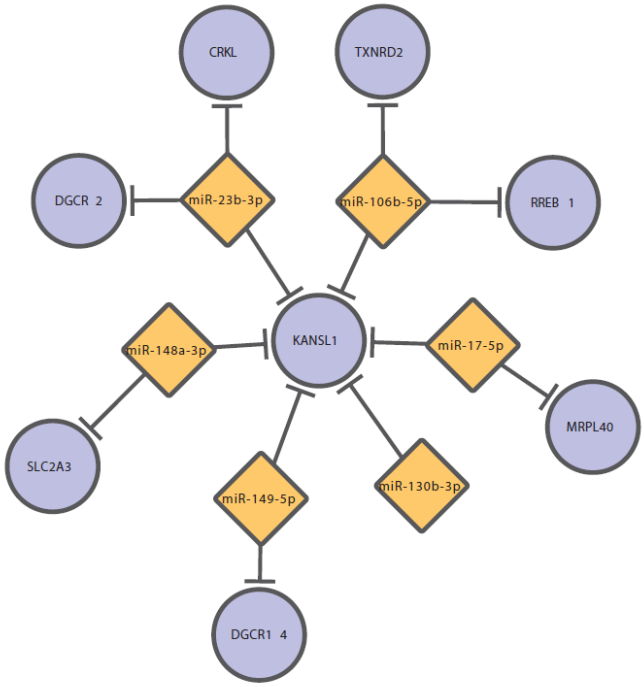

Figure 3: miRNA-mRNA interaction networks. The yellow diamonds represent miRNAs and the purple, mRNA targets. The edge connecting two nodes indicate regulation. Sub-network showing KANSL1 interacting module (From Leon L et al, in review).

2.2.3 Ancestry. Controlling for ancestry is relevant in large genomic studies. We performed Affymetrix SNP 6.0 arrays in 60 new patients and integrated it with our previous data from 213 samples, to assess for ancestry, using as HapMap as reference for European, Asian and African populations and Mao et al (AJHG 2007) for Ameridians. This work was done in collaboration with Drs S Eyheramendy at P. Universidad Católica and C. Vial at U del Desarrollo. Since patients´ place of birth was similar to the general geographic distribution in the country, the global ancestry results probably reflect the genetic ancestry of Chileans, showing that, on average, individuals had 45% of markers of Amerindian origin, 52% European and 3% African. These results gave rise to a more general and high impact article (Eyheramendy et al Nature Communications 2015[2]). Subsequently, we analyzed ancestry for the 22q11 cohort alone. Results of global ancestry are summarized in the Annexes section. Since the Chileans are an admixed population, work is currently underway to perform local ancestry analysis and to use admixture mapping in search for modifiers.

Student participation. Fernanda Rozas, MD, PhD(c) did one of her "Unidades de Investigación" of her PhD program in Medical Sciences, on ancestry determination and admixture mapping[3].

[2] This article was considered as "Other products" in the 2015 partial report. Nevertheless, ancestry estimations of the cohort was a part of this proposal (See Methods and Gantt chart), more than half of the participants in the article were from this cohort,, and it was accepted as a direct product for Fondecyt # 11110397, that contributed with a third of the patients. Given this, we consider that it should be considered a direct product of this grant

[3] The participation of a PhD student in Unidad de Investigación instead of a thesis was requested to and approved by FONDECYT. The pertinent documents (request, authorization, Summary and certificate) are in the Annexes section.

2.3. Rare variants identified through whole exome sequencing (WES)
Sixty 22q11DS samples (of 40 proposed in the original grant submission): 25 cases with conotruncal severe CHD (tetralogy of Fallot (TOF), TOF with pulmonary atresia (TOF+PA) or interrupted aortic arch (IAA), and 35 controls with normal cardiac phenotype were submitted for high throughput whole exome sequencing (WES) to the Northwest Genome Center (NWGC) (http://nwgc.gs.washington.edu). WES was perfomed using Roche's Nimblegen V2 Exome capture and 75 bp paired-end sequencing in HiSeq 2500 Illumina equipment. Two samples (both IAA cases) failed post sequencing quality controls and were removed from the analyses. Eight additional samples were sequenced in our center Nextera Rapid Capture Exome (Illumina) in a MiSeq Illumina sequencer. Given the lower throughput of this equipment, average read depth in our lab was 27x, compared with the >100x obtained at the NWGC, so these 8 samples were excluded from the analysis. |
Data was available for bioinformatics analysis in July 2016. This was performed by B Rebolledo, PhD. On average, each sample yielded 51.7 ± 13.6 million reads (mean±sd, range 40-110 million), with 66.5±1.5% of nucleotide calls over a PHRED score of 30 (0.1% error rate). Sequencing reads were aligned with the BWA-mem algorithm (v.0.7.15-r1140) against the hg38 human genome reference. Aligned reads were sorted, and duplicate-marked with Picard tools (v.2.5.0) prior to variant calling with Freebayes (v.1.0.2-58-g054b257). All 58 alignments were fed to the program, and set the minimum coverage of a site to be considered for variant detection at 10x, the minimum alignment quality at 20 (PHRED scale, error of 1%), and the minimum base quality PHRED score of 30. This generated a total of 547,568 raw variants. We further selected variants with quality over 30 and at least 47 out of the 58 samples (80%) with site coverage over 10x, to guarantee the quality of the calls. These additional filters led to 222,760 variants. After removing the sex chromosomes (due to the limitation of the computational tools handling the difference un ploidy of males and females) 218,898 variants were left, of which 206,271 corresponded to single nucleotide variants (SNVs), and 10,663 to INDELS. The overall proportion of variant sites was similar between cases and controls. Among the genes with higher proportion of variants of any type in cases compared to controls, two stand out:

Gene	Function	Additional information	N variants per gene	% Cases	% Controls	P-value (Z-test)
STX2	Vesicle metabolism	Ectoderm development/ Aorticopulmonary septum (ectodermal)	12	36%	3%	5.30E-04
WBSCR22	RNA methyltransferase	Williams-Beuren Syndrome / Heart defects	9	27%	0%	7.40E-04

Several of the variants in these genes are intronic, therefore not seen in our prior GWAS. These results will require replication in the wider cohort and functional analysis of pertinent variants. Further analysis is underway, facilitated by the incorporation of a bioinformatician to the team, and the acquisition of a computational cluster through FONDEQUIP.

In summary, this project has produced clinically relevant data, showing high case fatality rate for children with 22q11DS and cardiac defects, exceeding that of similar but non-syndromic CHD, and corroborated the development of movement disorders in adults. In terms of modifiers, we have excluded deletion size as a source of phenotypic variation; we have shown that a common variation in GPR98 and KANSL1 show significant association with the presence of CHD. These are interesting candidates that will need to be explored in functional studies: GPR98 is close to MEFC2, a gene that participates in cardiac development; KANSL1 regulates histone modifications and is part of miRNA regulatory network with CRKL, a gene within the deletion region. We have also found increased proportion of rare variants in STX2 and WBSCR22 in cases. These results suggest that variation in several genes may contribute to the presence of CHD in 22q11 DS patients.
The project also allowed our Center to grow in its high throughput sequencing capabilities, bioinformatics analysis of exome data, training of Medical and PhD students, as well as strengthening of our international collaborations. Specifically, we are now part of the International Consortium on Brain and Behavior in 22q11.2 Deletion Syndrome, NIH grant #5U01MH101723. These processes have resulted in improved results and high impact publications, and to support the local 22q11DS Foundation and the clinicians and educators that provide care for the patients and families.

PRODUCTOS

ARTÍCULOS

Para trabajos en Prensa/ Aceptados/Enviados adjunte copia de carta de aceptación o de recepción.

Nº : 1
Autor (a)(es/as) : Repetto GM; Guzman ML; Delgado I; Loyola H; Palomares M; Lay-Son G; Vial C; Benavides F; Espinoza K; Alvarez P .
Nombre Completo de la Revista : British Medical Journal Open
Título (Idioma original) : Case fatality rate and associated factors in 22q11 microdeletion syndrome patients. A retrospective cohort study
Indexación : ISI
ISSN :
Año : 2014
Vol. : 4
Nº : 11
Páginas : e005041
Estado de la publicación a la fecha : Publicada
Otras Fuentes de financiamiento, si las hay :

Envía documento en papel : no
Archivo(s) Asociado(s) al artículo :
Repetto_et_al_Case_fatality_rate_BMJ_Open_2014.pdf
https://servicios.conicyt.cl/sial/index.php/investigador/f4_articulos/descarga/8795354/1130392/2016/92246/1/

Nº : 2
Autor (a)(es/as) : Eyheramendy S, Martinez FI, Manevy F, Vial C, Repetto GM.
Nombre Completo de la Revista : Nature Communications
Título (Idioma original) : Genetic structure characterization of Chileans reflects historical immigration patterns.
Indexación : ISI
ISSN :
Año : 2015
Vol. : 6
Nº :
Páginas : 6472-81
Estado de la publicación a la fecha : Publicada
Otras Fuentes de financiamiento, si las hay :

Envía documento en papel : no
Archivo(s) Asociado(s) al artículo :
Eyheramendy_et_al_Genetic_characterization_Nature_Comms_2015.pdf
https://servicios.conicyt.cl/sial/index.php/investigador/f4_articulos/descarga/8795354/1130392/2016/92247/1/

Nº : 3
Autor (a)(es/as) : Butcher,NJ; Marras C; ... Repetto, GM; ...Bassett,AS
Nombre Completo de la Revista : Brain
Título (Idioma original) : Neuroimaging and clinical features in adults with a 22q11.2 deletion at risk of Parkinson's disease
Indexación : ISI
ISSN :
Año :
Vol. :
Nº :
Páginas :
Estado de la publicación a la fecha : Aceptada
Otras Fuentes de financiamiento, si las hay :

Envía documento en papel : no
Archivo(s) Asociado(s) al artículo :
Gmail___Fwd__Fw__Brain___Decision_on_Manuscript_ID_BRAIN_2016_01775.pdf
https://servicios.conicyt.cl/sial/index.php/investigador/f4_articulos/descarga/8795354/1130392/2016/92249/1/

Butcher_et_al._2016_Mechanism_and_markers_of_PD_in_22q11_.2DS_submitted_Brain_.pdf
https://servicios.conicyt.cl/sial/index.php/investigador/f4_articulos/descarga/8795354/1130392/2016/92249/2/

Nº : 4
Autor (a)(es/as) : León, LE; Benavides, F; Espinoza, K; Vial, C; Alvarez, P; Palomares, M; Lay-Son, G; Miranda, M; Repetto, GM
Nombre Completo de la Revista : Scientific Reports
Título (Idioma original) : Partial microduplication in the histone acetyltransferase complex member KANSL1 is associated with congenital heart defects in Chilean patients with 22q11.2D
Indexación : ISI
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Páginas :
Estado de la publicación a la fecha : Enviada
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LLeon_KANSL_1_Scientific_Reports_129011_0_art_file_3557319_hhrt8s.pdf
https://servicios.conicyt.cl/sial/index.php/investigador/f4_articulos/descarga/8795354/1130392/2016/92254/1/

Nº : 5
Autor (a)(es/as) : Guo, T; Repetto, GM; .... Morrow, BE
Nombre Completo de la Revista : Circulation: Cardiovascular Genetics
Título (Idioma original) : Genome-wide association study to find modifiers for tetralogy of Fallot in 22q11.2DS identifies variants in the GPR98 locus on 5q14.3
Indexación : ISI
ISSN :
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Nº :
Páginas :
Estado de la publicación a la fecha : Enviada
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Guo_et_al_GWAS_Cir_CVG_1_.pdf
https://servicios.conicyt.cl/sial/index.php/investigador/f4_articulos/descarga/8795354/1130392/2016/92256/1/

OTRAS PUBLICACIONES / PRODUCTOS

Nº : 1
Autor (a)(es/as) : Fung LAF; Butcher NJ; ---- Bassett AS.
Título (Idioma original) : Practical guidelines for managing adults with 22q11.2 deletion syndrome
Tipo de publicación o producto : Otros **Especificar :** Articulo cientifico

ISBN :
Editor (es) (Libro o Capitulo de libros) : Genetics in Medicine
Nombre de la editorial /Organización : American College of Medical Genetics and Genomics
País : ESTADOS UNIDOS DE AMERICA
Ciudad :
Fecha : Agosto - 2015
Año : 2015
Vol. : 17
Nº : 8
Páginas : 599-609
Otras Fuentes de financiamiento, si las hay :

Envía documento en papel : no
Archivo(s) Asociado(s) al artículo :
Fung_et_al_22q11_adult_guidelines_GIM_2015.pdf
https://servicios.conicyt.cl/sial/index.php/investigador/f4_otras_publicaciones/descarga/8795354/1130392/2016/27074/1/

Nº : 2
Autor (a)(es/as) : Repetto, G
Título (Idioma original) : Síndrome de deleción del cromosoma 22: una condición común pero poco conocida
Tipo de publicación o producto : Otros **Especificar :** Artículo en revista de difusión

ISBN :
Editor (es) (Libro o Capitulo de libros) : Dirección de Investigación
Nombre de la editorial /Organización : Universidad del Desarrollo
País : CHILE
Ciudad : Santiago
Fecha : Abril - 2016
Año : 2016
Vol. : 2
Nº : 2
Páginas : 4-9
Otras Fuentes de financiamiento, si las hay :

Envía documento en papel : no
Archivo(s) Asociado(s) al artículo :
revista_Investigacion_UDD___22q_abril_2016.pdf
https://servicios.conicyt.cl/sial/index.php/investigador/f4_otras_publicaciones/descarga/8795354/1130392/2016/27075/1/

Nº : 3
Autor (a)(es/as) : Lay-Son, G; Repetto, G
Título (Idioma original) : Estudio Genetico y Genomico en Pediatria
Tipo de publicación o producto : Otros **Especificar :** Artículo en revista de difusión

ISBN :
Editor (es) (Libro o Capitulo de libros) : Fernando Cádiz
Nombre de la editorial /Organización : Depto Cientifico Docente, Clínica Alemana de Santiago
País : CHILE
Ciudad : Santiago
Fecha : Diciembre - 2016
Año : 2016
Vol. : 6
Nº : 6
Páginas : 74-79
Otras Fuentes de financiamiento, si las hay :

Envía documento en papel : no
Archivo(s) Asociado(s) al artículo :
Lay_Son_Repetto_Estudio_Genetico_y_Genomico_en_Pediatria_Contacto_Cientifico_CAS_2016.pdf
https://servicios.conicyt.cl/sial/index.php/investigador/f4_otras_publicaciones/descarga/8795354/1130392/2016/27076/1/

Nº : 4
Autor (a)(es/as) : Johnston HR; Chopra P; Wingo TS; Patel V1; International Consortium on Brain and Behavior in 22q11.2 Deletion Syndrome;...; Cutler DJ
Título (Idioma original) : PEMapper and PECaller provide a simplified approach to whole-genome sequencing
Tipo de publicación o producto : Otros **Especificar :** Articulo Cientifico

ISBN :
Editor (es) (Libro o Capitulo de libros) :
Nombre de la editorial /Organización : Proceedings of the National Academy of Sciences
País : ESTADOS UNIDOS DE AMERICA
Ciudad : New York
Fecha : Marzo - 2017
Año : 2017
Vol. : 114
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Archivo(s) Asociado(s) al artículo :
Johnston_IBBC_PNAS_2017.pdf
https://servicios.conicyt.cl/sial/index.php/investigador/f4_otras_publicaciones/descarga/8795354/1130392/2016/28193/1/

CONGRESOS

Nº : 1
Autor (a)(es/as) : Repetto GM; Vial C, Espinoza K; Benavides F; Guzman ML; Guo T
Título (Idioma original) : 22Q11.2 MICRODELETION SIZE IN CHILEAN PATIENTS AND ASSOCIATION WITH CLINICAL FEATURES
Nombre del Congreso : Annual Meeting of the American Society of Human Genetics
País : ESTADOS UNIDOS DE AMERICA
Ciudad : San Diego
Fecha Inicio : 16/10/2014
Fecha Término : 22/10/2014
Nombre Publicación :
Año :
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Nº :
Páginas :
Envía documento en papel : no
Archivo Asociado :
Abstract_Presentation_Repetto_ASHG_2014.pdf
https://servicios.conicyt.cl/sial/index.php/investigador/f4_congresos/descarga/8795354/1130392/2016/147390/1/

Repetto_ASHG_2014.pdf
https://servicios.conicyt.cl/sial/index.php/investigador/f4_congresos/descarga/8795354/1130392/2016/147390/2/

Nº : 2
Autor (a)(es/as) : Repetto, G; Benavides, F; Guo, T; Vial, C; Espinoza, K
Título (Idioma original) : Chromosome region 22q11 deletion size and its association with clinical features
Nombre del Congreso : Reunión Anual de la Sociedad de Biologia de Chile
País : CHILE
Ciudad : Puerto varas
Fecha Inicio : 25/11/2014
Fecha Término : 28/11/2014
Nombre Publicación :
Año :
Vol. :
Nº :
Páginas :
Envía documento en papel : no
Archivo Asociado :
Repetto_et_al_resumen_Soc_Biologia_2014.pdf
https://servicios.conicyt.cl/sial/index.php/investigador/f4_congresos/descarga/8795354/1130392/2016/147391/1/

Nº : 3
Autor (a)(es/as) : Eyheramendy S; Manevy F; Ramirez M; Vial C; Espinoza K; Rivera JC; Repetto G
Título (Idioma original) : GWAS on an admixed Chilean sample of Cases and Controls to identify the genetic bases of the phenotypic variability in 22q11 microdeletion syndrome.
Nombre del Congreso : 63rd Annual Meeting of the American Society of Human Genetics
País : ESTADOS UNIDOS DE AMERICA
Ciudad : Boston
Fecha Inicio : 22/10/2013
Fecha Término : 26/10/2013
Nombre Publicación : 2013 ASHG meeting Abstracts pdf
Año : 2013
Vol. : NA
Nº : NA
Páginas : 151
Envía documento en papel : no
Archivo Asociado :
Eyheramendy_et_al_GWAS_ancestry_2013.pdf
https://servicios.conicyt.cl/sial/index.php/investigador/f4_congresos/descarga/8795354/1130392/2016/147392/1/

Portada_63rd_Annual_ASHG_Meeting_Abstracts_2013.pdf
https://servicios.conicyt.cl/sial/index.php/investigador/f4_congresos/descarga/8795354/1130392/2016/147392/2/

Nº : 4
Autor (a)(es/as) : Repetto GM; Guzman ML; Palomares M; Lay-Son G; Vial C; Espinoza K; Loyola H
Título (Idioma original) : Mortality in patients with 22q11 microdeletion syndrome
Nombre del Congreso : 63rd Annual meeting of the American Society of Human Genetics
País : ESTADOS UNIDOS DE AMERICA
Ciudad : Boston
Fecha Inicio : 22/10/2013
Fecha Término : 26/10/2013
Nombre Publicación : 2013 ASHG meeting Abstracts pdf
Año : 2013
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Páginas : 421
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Archivo Asociado :
repetto_et_al_Mortality_ASHG_2013.pdf
https://servicios.conicyt.cl/sial/index.php/investigador/f4_congresos/descarga/8795354/1130392/2016/147393/1/

Portada_63rd_Annual_ASHG_Meeting_Abstracts_20131.pdf
https://servicios.conicyt.cl/sial/index.php/investigador/f4_congresos/descarga/8795354/1130392/2016/147393/2/

Nº : 5
Autor (a)(es/as) : Benavides F; Guzman ML, Lay-Son G, Repetto G
Título (Idioma original) : Sindrome de microdeleción 22q11: determinación del tamaño de la deleción y su correlación con el fenotipo
Nombre del Congreso : XLVI Reunion Anual de la Sociedad de Genética de Chile
País : CHILE
Ciudad : La Serena
Fecha Inicio : 07/11/2013
Fecha Término : 09/11/2013
Nombre Publicación : Libro de resumenes de la Reunion Anual de la Soc de Genetica de Chile
Año : 2013
Vol. : NA
Nº : NA
Páginas : 71
Envía documento en papel : no
Archivo Asociado :
Benavides_et_al_SOCHIGEN_2013.PDF
https://servicios.conicyt.cl/sial/index.php/investigador/f4_congresos/descarga/8795354/1130392/2016/147394/1/

Nº : 6
Autor (a)(es/as) : Repetto G.

Título (Idioma original) : Microdeleción de cromosoma 22q11: Analisis clinico y molecular
Nombre del Congreso : XLVI Reunion Anual de la Sociedad de Genética de Chile
País : CHILE
Ciudad : La Serena
Fecha Inicio : 07/11/2013
Fecha Término : 09/11/2013
Nombre Publicación : Libro de resumenes de la Reunion Anual de la Soc de Genetica de Chile
Año : 2013
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Páginas :
Envía documento en papel : no
Archivo Asociado :
Repetto_SOCHIGEN_2013.PDF
https://servicios.conicyt.cl/sial/index.php/investigador/f4_congresos/descarga/8795354/1130392/2016/147395/1/

Nº : 7
Autor (a)(es/as) : Repetto, GM; Leon L; Vial C; Espinoza K; Benavides F; Guzman ML
Título (Idioma original) : 22q11 microdeletion syndrome: association of congenital heart disease with copy number variants
Nombre del Congreso : 65th Annual Meeting of the American Society of Human Genetics
País : ESTADOS UNIDOS DE AMERICA
Ciudad : Baltimore
Fecha Inicio : 06/10/2015
Fecha Término : 10/10/2015
Nombre Publicación : Online Abstracts for the 65th Annual Meeting of the American Society of Human Genetics
Año : 2015
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Nº :
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Envía documento en papel : no
Archivo Asociado :
ASHG_2015_Abstract_Data_Proof.pdf
https://servicios.conicyt.cl/sial/index.php/investigador/f4_congresos/descarga/8795354/1130392/2016/147396/1/

Nº : 8
Autor (a)(es/as) : León; LBenavides, F;Espinoza, K;, Vial, C; Álvarez, P; Palomares M.; Repetto, G..
Título (Idioma original) : IDENTIFICACIÓN DE LA DUPLICACIÓN 17q21.31 COMO MODIFICADOR GENÉTICO DEL FENOTIPO CARDIACO EN PACIENTES CON SÍNDROME DE MICRODELECIÓN 22q11.2.
Nombre del Congreso : XLVIII REUNIÓN ANUAL SOCIEDAD DE GENÉTICA DE CHILE
País : CHILE

Ciudad : Valdivia
Fecha Inicio : 22/10/2015
Fecha Término : 24/10/2015
Nombre Publicación : Libro de Resumenes XLVIII REUNIÓN ANUAL SOCIEDAD DE GENÉTICA DE CHILE
Año : 2015
Vol. :
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Páginas : e13
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Archivo Asociado :
Sochigen_2015_L_Leon.pdf
https://servicios.conicyt.cl/sial/index.php/investigador/f4_congresos/descarga/8795354/1130392/2016/147397/1/

Nº : 9
Autor (a)(es/as) : Repetto, GM; Cuiza A; Guzman ML; Palomares M; Lay-Son G; Miranda M; Alvarez, P; Fritsch,R; Ornstein C;
Título (Idioma original) : PREMATUREZ Y BAJO PESO AL NACER SON COMUNES EN PERSONAS CON SÍNDROME DE MICRODELECIÓN DE CROMOSOMA 22q11.2.
Nombre del Congreso : XLVIII REUNIÓN ANUAL SOCIEDAD DE GENÉTICA DE CHILE
País : CHILE
Ciudad : Valdivia
Fecha Inicio : 22/10/2015
Fecha Término : 24/10/2015
Nombre Publicación : Libro de Resumenes XLVIII REUNIÓN ANUAL SOCIEDAD DE GENÉTICA DE CHILE
Año : 2015
Vol. :
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Archivo Asociado :
Sochigen_2015_G_Repetto.pdf
https://servicios.conicyt.cl/sial/index.php/investigador/f4_congresos/descarga/8795354/1130392/2016/147398/1/

Nº : 10
Autor (a)(es/as) : Repetto, G; Giugliano C; Guzman, ML; Palomares, M
Título (Idioma original) : Delecion 22 y asociacion con fisura labiopalatina
Nombre del Congreso : II simposio internacional de fisurados y malformaciones faciales
País : CHILE
Ciudad : Viña del Mar
Fecha Inicio : 08/10/2015
Fecha Término : 10/10/2015
Nombre Publicación :

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Nº :
Páginas :
Envía documento en papel : no
Archivo Asociado :
DeleciÃ³n_22_y_asociaciÃ³n_con_Fisura_Labiopalatina_(1).pdf
https://servicios.conicyt.cl/sial/index.php/investigador/f4_congresos/descarga/8795354/1130392/2016/147399/1/

Nº : 11
Autor (a)(es/as) : Repetto G; Morovic CG; Goldsshmied K; Guzman ML; Palomares M
Título (Idioma original) : Trastornos de Alimentacion y Deglución en Pacientes con deleción 22
Nombre del Congreso : II simposio internacional de fisurados y malformaciones faciales
País : CHILE
Ciudad : Viña del Mar
Fecha Inicio : 08/10/2015
Fecha Término : 10/10/2015
Nombre Publicación :
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Nº :
Páginas :
Envía documento en papel : no
Archivo Asociado :
AlimentaciÃ³n_en_Pacientes_con_DeleciÃ³n_22_en_Etapas_Tempranas.pdf
https://servicios.conicyt.cl/sial/index.php/investigador/f4_congresos/descarga/8795354/1130392/2016/147400/1/

Nº : 12
Autor (a)(es/as) : Repetto, GM; Fritsch, R; Fadic, R; Chaná, P; Ornstein, C; Juri, C; Kramer, V; Pruzzo, R; Amaral H; Ocampo, A
Título (Idioma original) : Sleep movement disorders in adults with 22q11.2 deletion: a new dopamine-related manifestation? A case report
Nombre del Congreso : 66th Annual Meeting of the American Society of Human Genetics
País : CANADA
Ciudad : Vancouver
Fecha Inicio : 18/10/2016
Fecha Término : 22/10/2016
Nombre Publicación : 66th Annual Meeting of the American Society of Human Genetics Abstract Book
Año : 2016
Vol. :
Nº :
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Archivo Asociado :
ASHG2016_posterabstracts_Repetto_et_al.pdf
https://servicios.conicyt.cl/sial/index.php/investigador/f4_congresos/descarga/8795354/1130392/2016/147479/1/

Nº : 13
Autor (a)(es/as) : Guo, T; Repetto, GM; .... Morrow, BE
Título (Idioma original) : Genome-wide association study of modifiers for tetralogy of Fallot in 22q11DS identifies variants in the GPR98 locus on 5q14.3
Nombre del Congreso : 66th Annual Meeting of the American Society of Human Genetics
País : CANADA
Ciudad : Vancouver
Fecha Inicio : 18/10/2016
Fecha Término : 22/10/2016
Nombre Publicación : 66th Annual Meeting of the American Society of Human Genetics Abstract Book
Año : 2016
Vol. :
Nº :
Páginas : 199
Envía documento en papel : no
Archivo Asociado :
Guo_et_al_ASHG2016_posterabstracts.pdf
https://servicios.conicyt.cl/sial/index.php/investigador/f4_congresos/descarga/8795354/1130392/2016/147480/1/

Nº : 14
Autor (a)(es/as) : Hestand, MS; Nowakowska, BA; ... Repetto G;... Vermeesch JR
Título (Idioma original) : Reverse phenotyping of whole-genome sequencing data from patients with 22q11.2 deletions identifies an extensive catalog of broader phenotypic variability and benign variation in pathogenic disease ge
Nombre del Congreso : The European Human Genetics Conference 2017
País : DINAMARCA
Ciudad : Copenhagen
Fecha Inicio : 27/05/2017
Fecha Término : 30/05/2017
Nombre Publicación :
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Envía documento en papel : no
Archivo Asociado :
ESHG_2017_abstract_final_Hestand_et_al.pdf
https://servicios.conicyt.cl/sial/index.php/investigador/f4_congresos/descarga/8795354/1130392/2016/148471/1/

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Nº : 15
Autor (a)(es/as) : Alvarez, P; Acevedo V; Navarro F; Rios P; Cuiza A, Poggi H; Repetto G
Título (Idioma original) : Chromosome 22q11.2 deletion syndrome: analysis of associations between cardiac and extracardiac malformations in a cohort of 276 patients
Nombre del Congreso : 7th World Congress of Pediatric Cardiology and Cardiac Surgery
País : ESPANA
Ciudad : Barcelona
Fecha Inicio : 16/07/2017
Fecha Término : 21/07/2017
Nombre Publicación :
Año :
Vol. :
Nº :
Páginas :
Envía documento en papel : no
Archivo Asociado :
World_Congress_Pediatric_Cardiology_P_Alvarez_2017.pdf
https://servicios.conicyt.cl/sial/index.php/investigador/f4_congresos/descarga/8795354/1130392/2016/148473/1/

Gmail___Fwd__WCPCCS_Notification_of_Acceptance_P_Alvarez.pdf
https://servicios.conicyt.cl/sial/index.php/investigador/f4_congresos/descarga/8795354/1130392/2016/148473/2/

TESIS/MEMORIAS

Sin información ingresada.

ANEXOS

Nº : 1
Archivo Asociado : Informe_de_Auditoria_Fondecyt_1130392_2017.pdf
https://servicios.conicyt.cl/sial/index.php/investigador/f5_anexos/descarga/8795354/1130392/2016/73110/

Nº : 2
Archivo Asociado : Difusion_a_la_Sociedad_1130392.pdf
https://servicios.conicyt.cl/sial/index.php/investigador/f5_anexos/descarga/8795354/1130392/2016/74084/

Nº : 3

Archivo Asociado : participacion_de_estudiantes.pdf

https://servicios.conicyt.cl/sial/index.php/investigador/f5_anexos/descarga/8795354/1130392/2016/74412/

A continuación se detallan los anexos físicos/papel que no se incluyen en el informe en formato PDF.