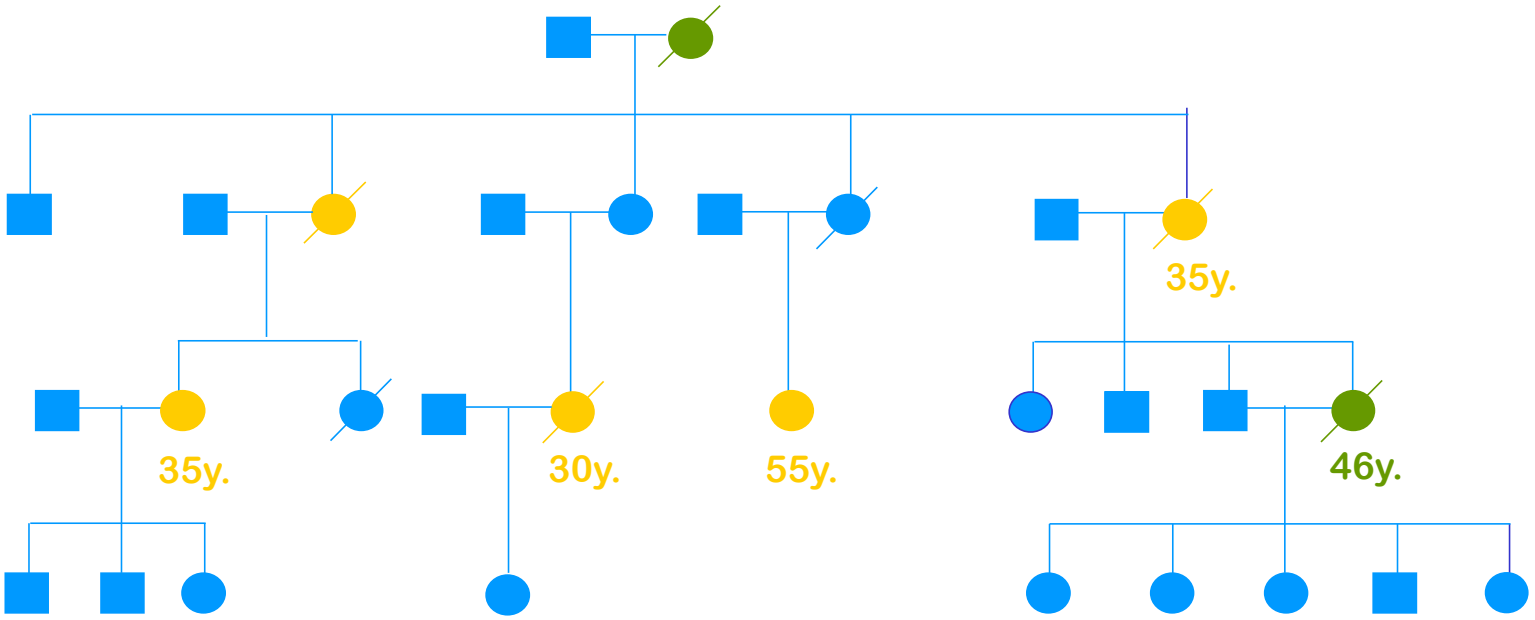
CÁNCER HEREDITARIO: INVESTIGACIÓN TRANSLACIONAL

Ana Osorio. Facultativo Servicio de Genética.

IV REUNIÓN ANUAL DEL ÁREA DE GENÉTICA Y GENÓMICA
DEL IIS-FJD
29 de septiembre 2022

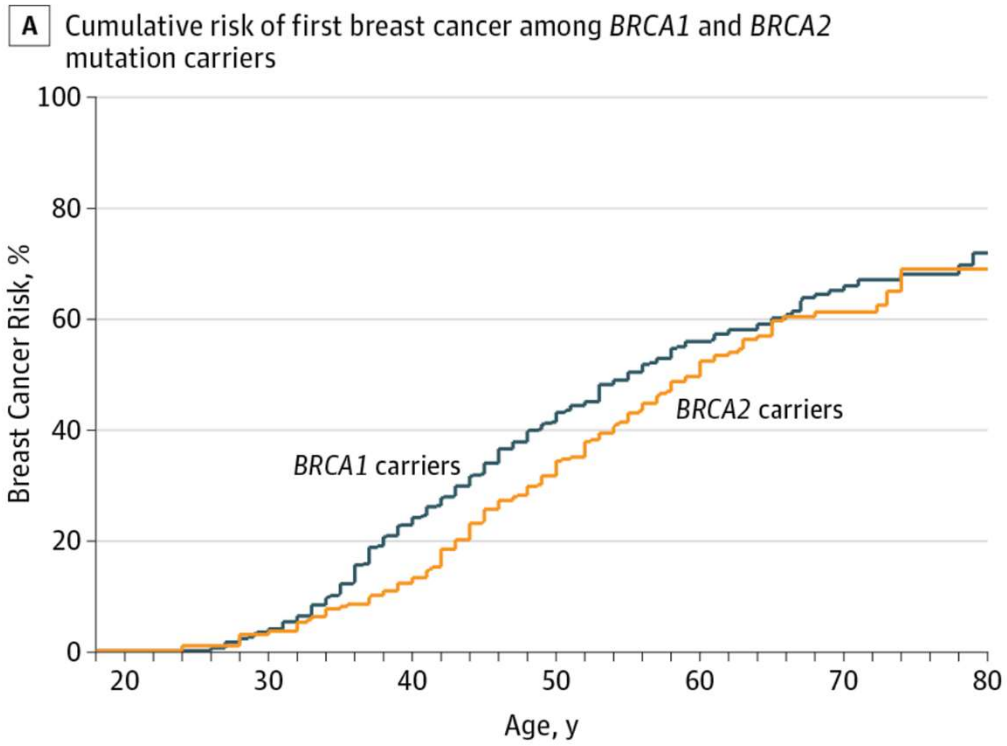
Hereditary Breast and Ovarian Cancer (HBOC)

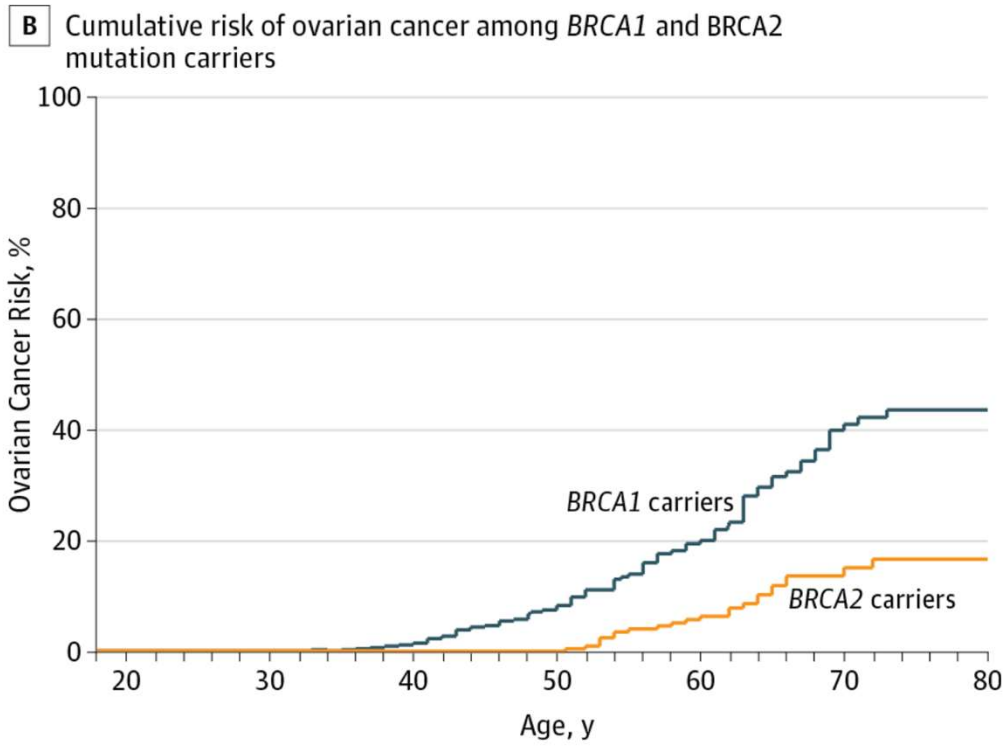


Breast cancer

Ovarian cancer

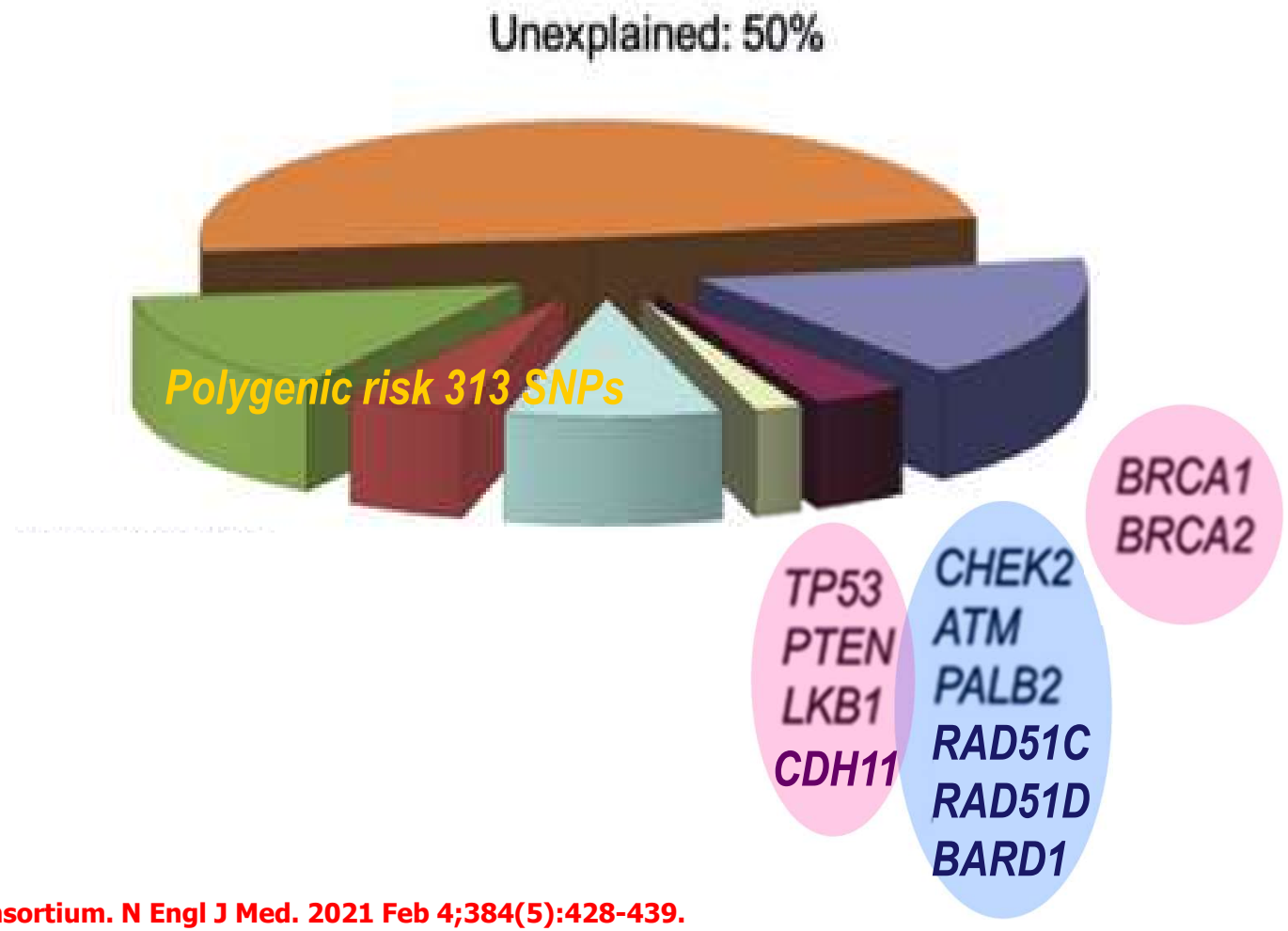
Cancer risks for *BRCA1* and *BRCA2* mutation carriers





Average cumulative risks by age 80 years. Prospective cohort study of 6036 *BRCA1* and 3820 *BRCA2* female carriers. Kuchenbaecker et a., JAMA. 2017 Jun 20;**317**(23):2402-2416.

Breast cancer susceptibility: current model



Breat Cancer Association Consortium. N Engl J Med. 2021 Feb 4;384(5):428-439.

Whole Exome Sequencing in Familial Breast Cancer

Rosa-Rosa, et al., PLoS One 2010	**Spain**	**Not conclusive**
Snape et al., Breast Cancer Res. Treat. 2011	**U.K.**	**Not conclusive**
Park et al., Breast Cancer Res. Treat. 2011	**Australia, US**	**Not conclusive**
Park et al., Am. J. Hum. Genet. 2012	**Netherlands, Australia & Spain**	***XRCC2?***
Thompson et al., Plos Genetics 2012	**Australia & New Zealand**	***FANCC & BLM?***
Hilbers et al., PLoS One 2013	**Netherlands**	**Not conclusive**
Gracia-Aznarez et al., Plos One 2013	**France, Italy, Netherlands, Australia & Spain**	**Not conclusive**
Lynch et al., Breast J 2013	**U.S.**	**Not conclusive**
Wen et al., BMC Cancer 2014	**U.S.**	**Not conclusive**
Park et al., Cancer Discovery 2014	**U.S. & Australia**	***RINT1?***
Kiiski et al., PNAS 2014	**Finland**	***FANCM?***
Cybulsky et al., Nat. Genet. 2015	**Poland & Quebec**	***RECQL?***
Sun et al., PLoS Genetics 2015	**China**	***RECQL?***
Noh et al., Radiat Oncol 2015	**Korea**	**Not conclusive**
Maatta et al., Eur J Human Genet 2017	**Finland**	**Not conclusive**
Jalkh et al., BMC Med Genomics 2017	**Lebanon**	**Not conclusive**
Kim et al., PLoS One 2017	**Egypt**	**Not conclusive**
Tavera-Tapia et al., Human Mutation 2019	**Spain**	***RECQL5?***
Felicio et al., 2021 et al., Human Mutation 2021	**Brazil**	**Not conclusive**

cnio stop cancer → iis FJD INSTITUTO DE INVESTIGACIÓN SANITARIA FUNDACIÓN JIMÉNEZ DÍAZ

Research projects:

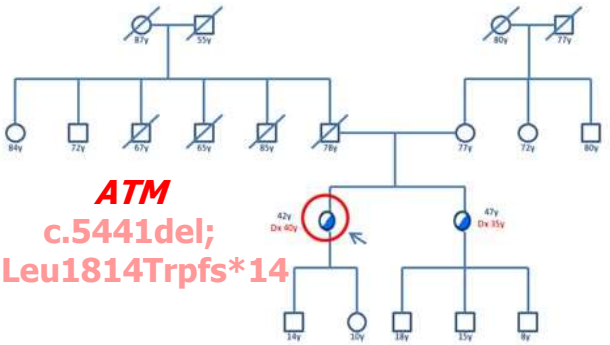
1. **Optimizing masive sequencing strategies for the identification and clinical translation of new susceptibility genes implicated in familial breast cancer (PI19/00640, 2019-2023).**
2. **Impact of incorporating PRS and mammographic density in BC risk stratification in *ATM, BARD1, CHEK2, RAD51C, RAD51D and PALB2* mutations carriers (Dr. de la Hoya, HCSC & GEICAM)**
3. **Exploring the mechanism of action of PARP inhibitors in *BRCA1/2* mutation carriers.**

Collaborations

1. **CIMBA consortium (Consortium of Investigators of Modifiers of BRCA1/2), Cambridge University.**
2. **MERGE (Male Breast Cancer Genetics Consortium), Belfast University.**
3. **IMPaCT-GENóMICA (WP4).**

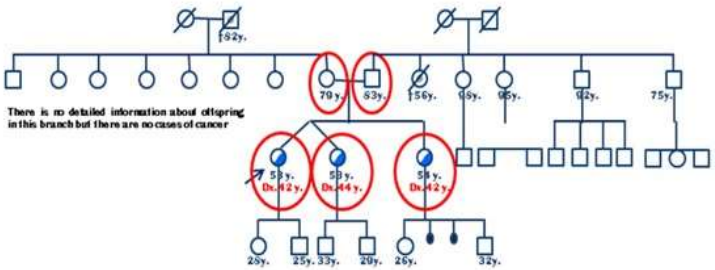
cnag 2013, 300 exomes to elucidate rare diseases

Family 1

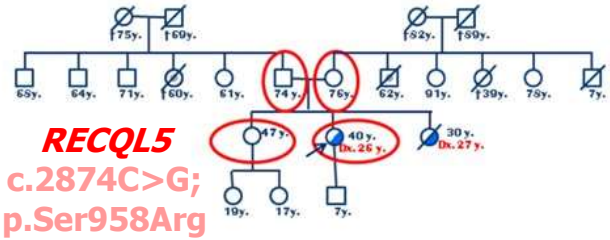


ATM
c.5441del;
p.Leu1814Trpfs*14

Family 3

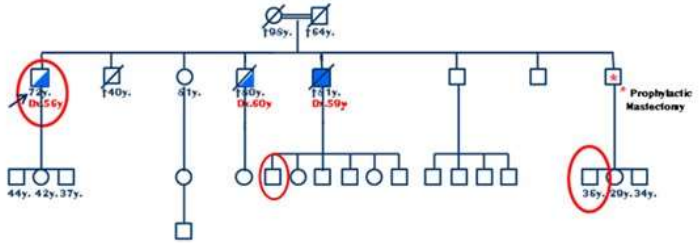


Family 2



RECQL5
c.2874C>G;
p.Ser958Arg

Family 4



Tavera-Tapia et al., Breast Cancer Res Treat. 2017 Feb;161(3):597-604
Tavera-Tapia et al., Hum Mutat. 2019 May;40(5):566-577

PI19/00640, 2019-2023

Patients:

- ✓ 2500 BRCAX families selected by phenotype. Minimum criteria: a) at least 2 women affected with BC, at least one <50y or b) at least one MBC. "Extreme" phenotypes were prioritized

- ✓ Proceeding from:
  - CNIO
  - Hospital Clínico San Carlos (Madrid)
  - Hospital La Mancha Centro (Ciudad Real)
  - Hospital General de Ciudad Real
  - Complejo Hospitalario de Albacete
  - Hospital Virgen de la Luz (Cuenca)
  - Universidad de Valladolid

Controls:

Data from ~50,000 European non-Finnish individuals (gnomAD v2.1.1)
Collaborative Spanish Variant Server (CSVS) (http://csvs.clinbioinfosspa.es/)

Genes

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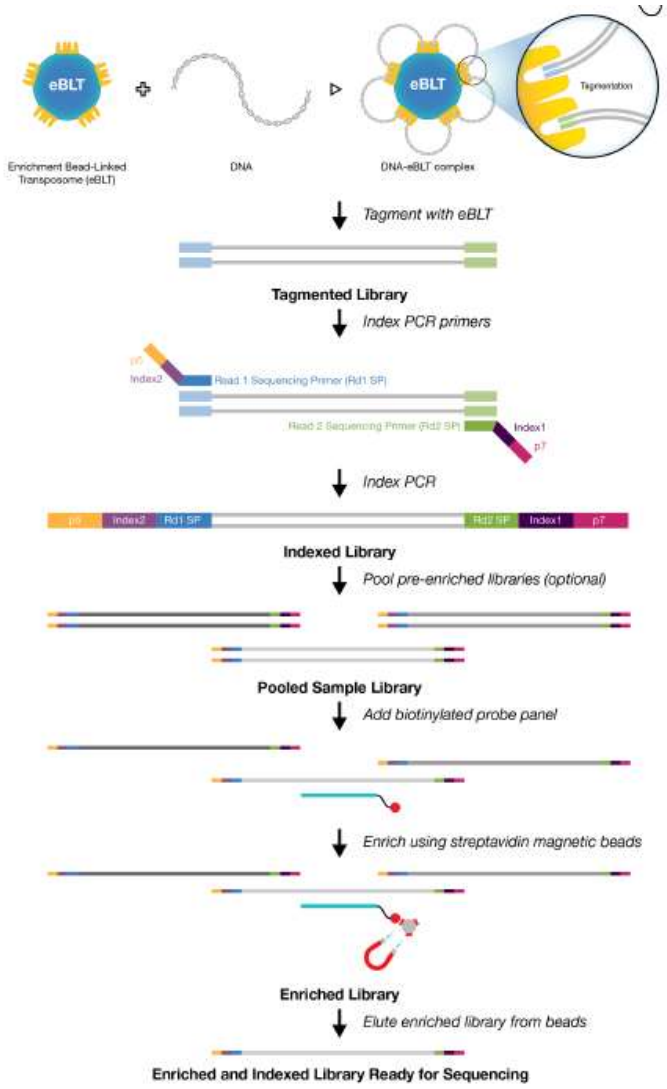
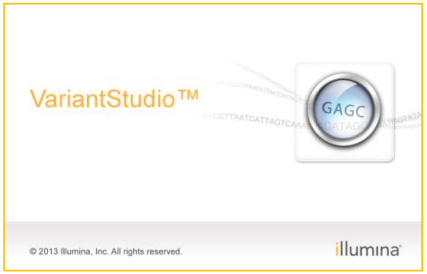
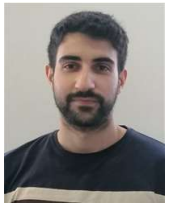
NGS using Nextera Flex for Enrichement with IDT probes



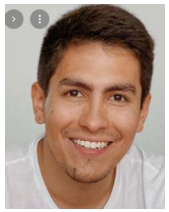


Anne Parra Heming
(Master student 2020)

Beatriz Benito Sánchez
(Master student 2021)



Erik Marchena Perea
(PhD student from 2021)



Milton Salazar Hidalgo
(Master student 2022)

MAIN RESULTS 1: HELICASES

cancers

MDPI

Article.

A large case-control study performed in Spanish population suggests that *RECQL5* is the only RECQ helicase involved in breast cancer susceptibility

Marchena-Perea EM[1], Salazar-Hidalgo M[1], Gómez-Sanz A[2], Arranz-Ledo M[3], Barroso A[1], Fernández V[1], Tejera-Pérez H[4], Pita G[4], Núñez-Torres R[4], Pombo L[5], Morales-Chamorro R[6], Cano-Cano JM[7], Soriano MC[8], Garre P[2], Durán M[3], Currás-Freixes M[1], de la Hoya M[2] and Osorio A[*1,9]

Future plans

- ✓ To finish the genetics analysis and the case-control studies for the new candidate genes (Erik Marchena`s PhD project to be finished in December 2022)

- ✓ To ask for funding to establish the role of the candidate BC susceptibility genes by.

    1. Performing structural and functional analysis of the candidate variants

    2. Validating the results in a new BRCAX series.

- ✓ To continue with all the collaborative projects (already preparing documents)