ELN European LeukemiaNet

ERIC european research initiative on CLL

WP7 CLL

TP53 Network activities

Minor clones, Recommendations' update & Database

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FAKULTNÍ NEMOCNICE BRNO
Interní hematologická a onkologická klinika FN Brno a LF MU
MUNI
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ACTIVITIES OF *TP53* NETWORK

- **Help laboratories keep high standards of *TP53* diagnostics in CLL**
  - ERIC *TP53* Certification (12 Certification rounds, >100 certified laboratories)
  - Cooperation with GenQA/NEQAS (re-certification)
  - Educational workshops
  - *TP53* Helpdesk
  - ERIC Recommendations on *TP53* Analysis in CLL
- **Respond to technical and therapeutical progress**
  - Detection of variants <5-10% VAF – methodical challenges, clinical impact, standardization
- **Transfer knowledge gained in routine *TP53* diagnostics in CLL to wide *TP53* community**
  - ERIC *TP53* database

ERIC MULTICENTER STUDY ON *TP53* VARIANTS BELOW 10% VAF

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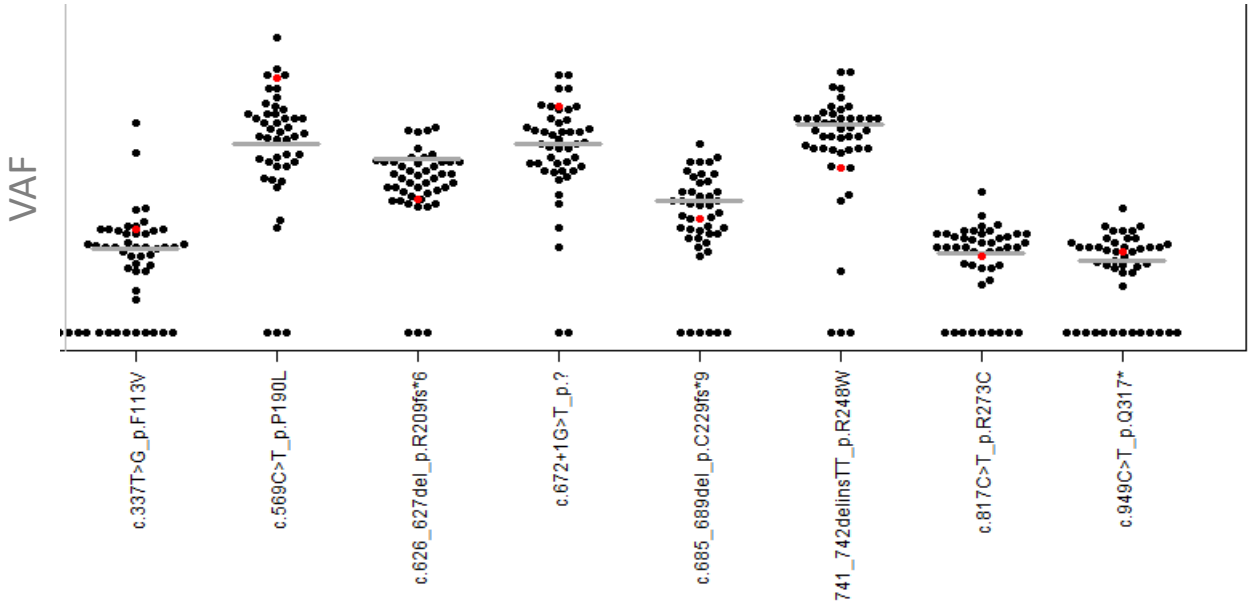
PART1: METHODICAL HARMONIZATION (41 participants)

Inter-laboratory comparison of NGS results obtained from the set of reference samples

- Invitation to the study by ERIC office – Q3/2018
- 7 samples with 23 variants <10% VAF prepared in Brno and Milan, sent Q2/2019
- Comparison of individual results with results of other groups
  - individual and summary reports Q4/2019
- EHA poster 2020
- **Manuscript preparation – in progress**

✓ 63% laboratories
no false positivity >2% VAF
no false negativity >2% VAF

× 17% laboratories
false positivity above their limit of detection



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PART 2: DATA COLLECTION (10 participants)

- Patient data collection – since 12/2020
- Data curation – Q4/2021
- **Data analysis – currently running**
- **Manuscript preparation**

Hospital Universitario 12 de Octubre, I+12, CNIO, Complutense University; Madrid; Spain
Hopital Avicenne AP-HP; Bobigny; France
Rigshospitalet, Copenhagen University Hospital; Copenhagen; Denmark
Centre for Research and Technology Hellas; Thessaloniki; Greece
National Research Center for Hematology; Moscow; Russia
Royal Bournemouth Hospital; Bournemouth; UK
iMM - Instituto de Medicina Molecular, Faculdade de Medicina; Lisboa; Portugal
IRCCS Ospedale San Raffaele and Università Vita-Salute San Raffaele; Milano; Italy
Vall d'Hebron Institute of Oncology, Vall d'Hebron University Hospital; Barcelona; Spain
University Hospital and Masaryk University Brno; Czech Republic

≈1000 patients

ERIC *TP53* DATABASE

ERIC *TP53* DATABASE

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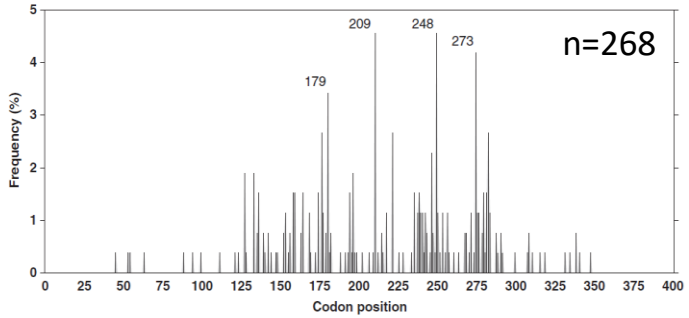
PROJECT AIMS

- To collect a list of *TP53* variants obtained during routine *TP53* screening in CLL
- To create a publicly accessible CLL-specific database of curated *TP53* variants
- Analyze the disease-specific variant profile (update Zenz et al., Leukemia 2010)
- Analyze the association with clinico-biological parameters (treatment, FISH, IGHV,...)
- **Help diagnosticians to asses the clinical impact of detected variants**



WHY?

- Current TP53 databases – gene specific databases, only published data - risk of redundancies
  - The TP53 database originally IARC) https://TP53.isb-cgc.org/
  - UMD TP53 database (http://p53.fr/
- CLL is the first malignancy for which testing for the presence of *TP53* defects is fully implemented in the clinics to guide treatment decision-making.

REQUIRED DATA

- **Data on *TP53* variants** (variant description, VAF...)
  - All detected variants irrespective of their functional impact
  - Except for the most common polymorphisms

- **Brief method description** (sample type, sequencing method...)

- **Clinical data – part of ERIC CLL database**
  - Not obligatory but highly welcomed
  - In centers involved in ERIC CLL database – data will be linked based on patient ID

ERIC *TP53* DATABASE

- Addressing participants Q3-4/2020
- **Collecting data – Q1-2/2022**
- Data curation – Q2-Q3/2022
- Data analysis – since Q4/2022
- Releasing the database – 2023
- Preparing a manuscript – 2023

Current state: 45 participants (22 countries)

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YOU ARE STILL WELCOMED TO JOIN

HOW TO APPLY:

1) Via application questionnaire (ERIC members received an email with the link):
https://barcelo.eventsair.com/eric-members-database/database-of-TP53-variants-in-cll/Site/Register

2) Contact ERIC office or malcikova.jitka@fnbrno.cz

- ERIC *TP53* certification required

Project description: http://www.ericll.org/projects/

SUB-PROJECT
FUNCTIONAL ANALYSIS OF IN-FRAME VARIANTS

- Deletions and insertions in the *TP53* gene not resulting in frameshift (≈ 5% of *TP53* mutations)
- Pathogenic interpretation is more experience-based than evidence-based
- Very limited solid evidence in literature exists

AIM

- To collect the set of inframe variants within the *TP53* database and analyze their functional impact using Functional analysis in yeast
- REQUIREMENTS: cDNA or RNA of sufficient quality

ERIC RECOMMENDATIONS ON *TP53* ANALYSIS - UPDATE

Do we still need *TP53* analysis in the era of targeted treatment?

- ESMO guidelines recommend targeted treatment for all IGHV unmut patients *(Eischhorst et al., Ann Oncol 2021)*
- **BUT** *TP53* status remains crucial in treatment-decision algorithms in many countries
- Different type of targeretd treatment for TP53-mut patients?

„Analysis of *TP53* defects - life saving“

Do we need new recommendations?

Current recommendations written in 2017 – what has changed?

- 2022 NGS prevails
  - New technical aspects
  - Detection of minor clones below the detection limit of Sanger sequencing - high risk of clonal selection upon CIT

Malcikova et al., Leukemia 2018	**Update**
Sanger and NGS equal	NGS preferred (but Sanger better than nothing)
Do not report mutations <5-10% VAF	All variants RELIABLY identified may be reported?
	Extending resources for variant interpretation
	Increasing demands for reporting format

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THANK YOU VERY MUCH FOR YOUR ATTENTION

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