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BRIEF COMMUNICATION

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The JAK3^{Q988P} mutation reveals oncogenic potential and resistance to ruxolitinib

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Abstract

T-cell acute lymphoblastic leukemia (T-ALL) arises from the malignant transformation of T-cell progenitors at various differentiation stages. Given that patients who relapse have a dismal prognosis, there is an urgent need to identify the molecular alterations that are present in such patients and promote leukemogenesis to implement personalized therapies with higher efficacy and fewer adverse effects. In the present manuscript, we identified the JAK3^{Q988P} mutation in a T-ALL patient who did not achieve a durable response after the conventional treatment and whose tumor cells at relapse presented constitutive activation of the JAK/STAT pathway. Although JAK3^{Q988P} has been previously identified in T-ALL patients from different studies, the functional consequences exerted by this mutation remain unexplored. Through the combination of different hematopoietic cellular models, we functionally characterize JAK3^{Q988P} as an oncogenic mutation that contributes to leukemogenesis. Notably, JAK3^{Q988P} not only promotes constitutive activation of the JAK/STAT pathway in the absence of cytokines and growth factors, as is the case for other *JAK3* mutations that have been functionally characterized as oncogenic, but also functions independently of JAK1 and IL2RG, resulting in high oncogenic potential as well as resistance to ruxolitinib. Our results indicate that ruxolitinib may not be efficient for future patients bearing the JAK3^{Q988P} mutation who instead may

Abbreviations: dbGaP, genotypes and phenotypes database; JAK/STAT, Janus kinase/signal transducers and activators of transcription; NCI, National Cancer Institute; TARGET, therapeutically applicable research to generate effective treatments; T-ALL, T-cell acute lymphoblastic leukemia.

obtain greater benefits from treatments involving other pharmacological inhibitors such as tofacitinib.

KEYWORDS
JAK/STAT, JAK3, ruxolitinib, T-ALL

T-cell acute lymphoblastic leukemia (T-ALL) arises from the malignant transformation of T-cell progenitors at various differentiation stages.[1] Current standard-of-care treatments for T-ALL achieve reasonable rates of initial complete responses and mainly consist of high-dose multiagent chemotherapy that may be followed by hematopoietic stem cell transplantation in high-risk patients.[2] However, those patients who relapse have a dismal prognosis and cure rates drop below 10%. This is partly due to a lack of therapeutic options because no pharmacological inhibitors have been implemented for relapse T-ALL patients since the approval of neralabine in 2005.[3] Therefore, thoroughly studying the landscape of molecular alterations that are present in such patients and contribute to leukemogenesis becomes essential for the development of novel personalized-therapies with greater efficacy and fewer side effects.[4,5]

Here, we comprehensively characterize the JAK3^{Q988P} mutation that was identified in an adult male diagnosed with T-ALL who did not achieve a durable response after conventional treatments. We performed exome sequencing of the tumor cells at relapse (Patient_Rx) to detect mutations in relevant proto-oncogenes and tumor suppressor genes susceptible of contributing to leukemogenesis in T-ALL (Figure S1A).

Among the identified mutations, we specifically focused on *JAK3* 1533G>A and *JAK3* 2963A>C since some *JAK3* mutations have been recently associated with a low response to induction chemotherapy.[6] Additionally, the simultaneous presence of different mutations in *JAK3* has been proposed as a mechanism that promotes constitutive activation of the JAK/STAT pathway in T-ALL.[7] Therefore, we confirmed by Sanger sequencing the presence of both *JAK3* mutations in Patient_Rx (Figure 1A). Consistent with data from exome sequencing, these mutations are heterozygous and appear as two different peaks for the same position in the electropherogram. Moreover, we observed that both mutations occur in the same allele of *JAK3* (Figure S1B). Notably, only *JAK3* 1533G>A was present in the tumor cells at diagnosis, postulating *JAK3* 2963A>C as a subsequent alteration that is limited to Patient_Rx and that emerged de novo or due to clonal evolution (Figure S1C). Additionally, 1533G>A and 2963A>C are missense mutations that result in the substitution of methionine by isoleucine at position 511 (JAK3^{M511I}) and in the substitution of glutamine by proline at position 988 (JAK3^{Q988P}), respectively (Figure 1B). To determine whether signaling through the JAK/STAT pathway may be relevant for Patient_Rx, we performed RNA-seq and analyzed the expression levels of genes belonging to JAK and STAT families (Figure 1C and Figure S2A). Our results showed that most of them, including *JAK3*, were overexpressed in Patient_Rx compared to control thymocytes. We then analyzed the expression levels for multiple genes previously reported as transcriptional targets of activated STAT proteins (specifically: *CISH*, *OSM*, *MYC*, *PIM1*, *VEGFA*, *MMP2*, *MMP2*, *MMP9*, *IL4R*, *CCND1*, *BCL2L1*, *XBP1*, and *LIF*) and observed that most of them were also overexpressed (Figure 1D and Figure S2B). Additionally, we evaluated *CISH* and *LIF* expression levels, which are considered hallmarks of JAK/STAT pathway activation, in the context of 272 T-ALL cases and Patient_Rx was ranked in the highest quartile (Figure 1E,F). Altogether, our results indicate a constitutive activation of the JAK/STAT pathway in Patient_Rx.

We investigated whether the *JAK3* mutations that we had previously identified could be responsible for constitutively activating the JAK/STAT pathway in Patient_Rx. At this respect, JAK3^{M511I} has been previously reported as oncogenic.[8] In contrast, the functional consequences of JAK3^{Q988P} remain unexplored even though it is a mutation that has been previously identified in T-ALL patients from different studies.[7,9–11] To determine whether JAK3^{Q988P} is oncogenic and contributes to leukemogenesis, we performed an in silico analysis with three different predictors that catalogued JAK3^{Q988P} as a likely-oncogenic mutation (Figure S2C). We experimentally validated such hypothesis by analyzing the ability of JAK3^{Q988P} to induce growth and viability of Ba/F3 cells in the absence of cytokines and growth factors (Figure 1G). Cells expressing JAK3^{Q988P} showed significantly higher levels of growth and viability than untransduced or JAK3^{WT}-transduced cells. Furthermore, these results correlated with increased levels of STAT5-phosphorylation, indicating that JAK3^{Q988P} is an oncogenic mutation that promotes constitutive activation of the JAK/STAT pathway in the absence of cytokines and growth factors (Figure 1H). The oncogenic role of JAK3^{Q988P} was further confirmed in M07e cells (Figure S2B, S2D, S2E).

JAK3 mutations are the most frequent genetic alteration involving a member of the JAK/STAT pathway in T-ALL.[12] Consequently, numerous mutations have been identified along the different regions that constitute the *JAK3* gene (Figure 2A). However, the oncogenic potential of *JAK3* mutations is highly heterogeneous and only a limited fraction of them have been functionally characterized as oncogenic while the rest are either considered passenger mutations or their functional consequences remain unexplored (Figure 2B left circle).[13–15] Moreover, it is plausible that not all *JAK3* mutations functionally characterized as oncogenic contribute to leukemogenesis through identical molecular mechanisms. Unlike most *JAK3* oncogenic mutations, JAK3^{Q988P} does not affect the pseudokinase domain but the kinase domain, where two other mutations (JAK3^{L857P} and JAK3^{L875H}) are able to activate the JAK/STAT pathway independently of JAK1 and IL2RG proteins (Figure 2B right circle, C). To

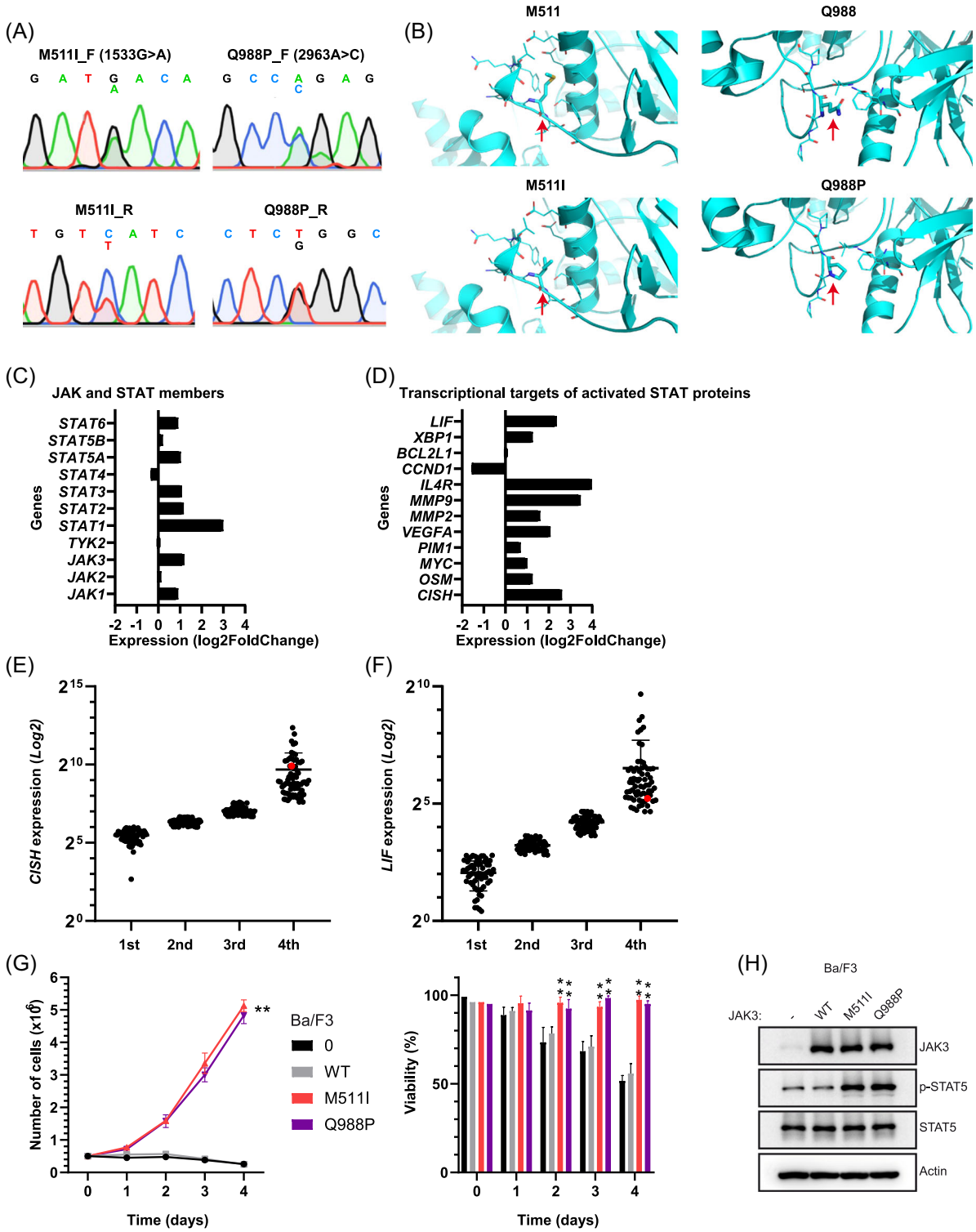

FIGURE 1 Characterization of JAK3^{Q988P} as an oncogenic mutation. (A) Electropherograms confirming the presence of the single-point mutations 1533G>A and 2963A>C in *JAK3*. (B) Bioinformatic model for the structure of JAK3 showing in detail Meteonin^{511} (left) and Glutamine^{988} (right) as well as their substitution by an isoleucine and a proline respectively. The structure of JAK3 has been plotted with Pymol. Color legend: carbons in cyan, oxygens in red, nitrogens in blue and sulfurs in yellow. (C) mRNA expression levels of genes belonging to JAK and STAT families in the tumor sample at relapse and referred to control thymocytes. (D) mRNA expression levels for multiple transcriptional targets of activated STAT proteins in the tumor sample at relapse and referred to control thymocytes. (E) Distribution of 272 T-ALL cases into quartiles according to *CISH* expression (DESeq. 2 normalized counts). The index case belongs to the fourth quartile (red dot). (F) Distribution of 272 T-ALL cases into quartiles according to *LIF* expression (DESeq. 2 normalized counts). The index case belongs to the fourth quartile (red dot). (G) Cell growth (left) and viability (right) assays of Ba/F3 cells untransduced (0) or transduced with JAK3^{WT} or JAK3 mutants. JAK3^{M511I} was used as a positive control. The graphics show the mean ± standard deviation (*SD*) after three independent experiments. *: $p < 0.05$; **: $p < 0.01$. (H) Western blot for JAK3, p-STAT5 and STAT5 in Ba/F3 cells untransduced (–) or transduced with JAK3^{WT} or JAK3 mutants. Images are representative examples of at least three independent experiments. mRNA, messenger RNA; T-ALL, T-cell acute lymphoblastic leukemia.

test whether this is also the case for JAK3^{Q988P}, we analyzed the ability of this mutation to induce constitutive activation of the JAK/STAT pathway in HEK293T cells, which are deficient in IL2RG, and in U4A cells, which are deficient in IL2RG and JAK1 (Figure 2D). In this case, JAK3^{L857P} serves as a positive control, whereas JAK3^{M511I} serves as a negative control since, like most *JAK3* mutations, it requires functionally active JAK1 and IL2RG proteins. Our results demonstrate that, in both cellular models, JAK3^{Q988P} induces STAT1-phosphorylation to a greater extent than JAK3^{M511I} and to a similar level than JAK3^{L857P}. We investigated the implications resulting from the ability of JAK3^{Q988P} to promote constitutive activation of the JAK/STAT pathway independently of JAK1 and IL2RG by assessing the sensitivity of JAK3^{Q988P} to ruxolitinib, a specific JAK1 inhibitor (Figure 2E). Our results demonstrate that, in terms of growth and viability, cells expressing JAK3^{Q988P} are less sensitive to

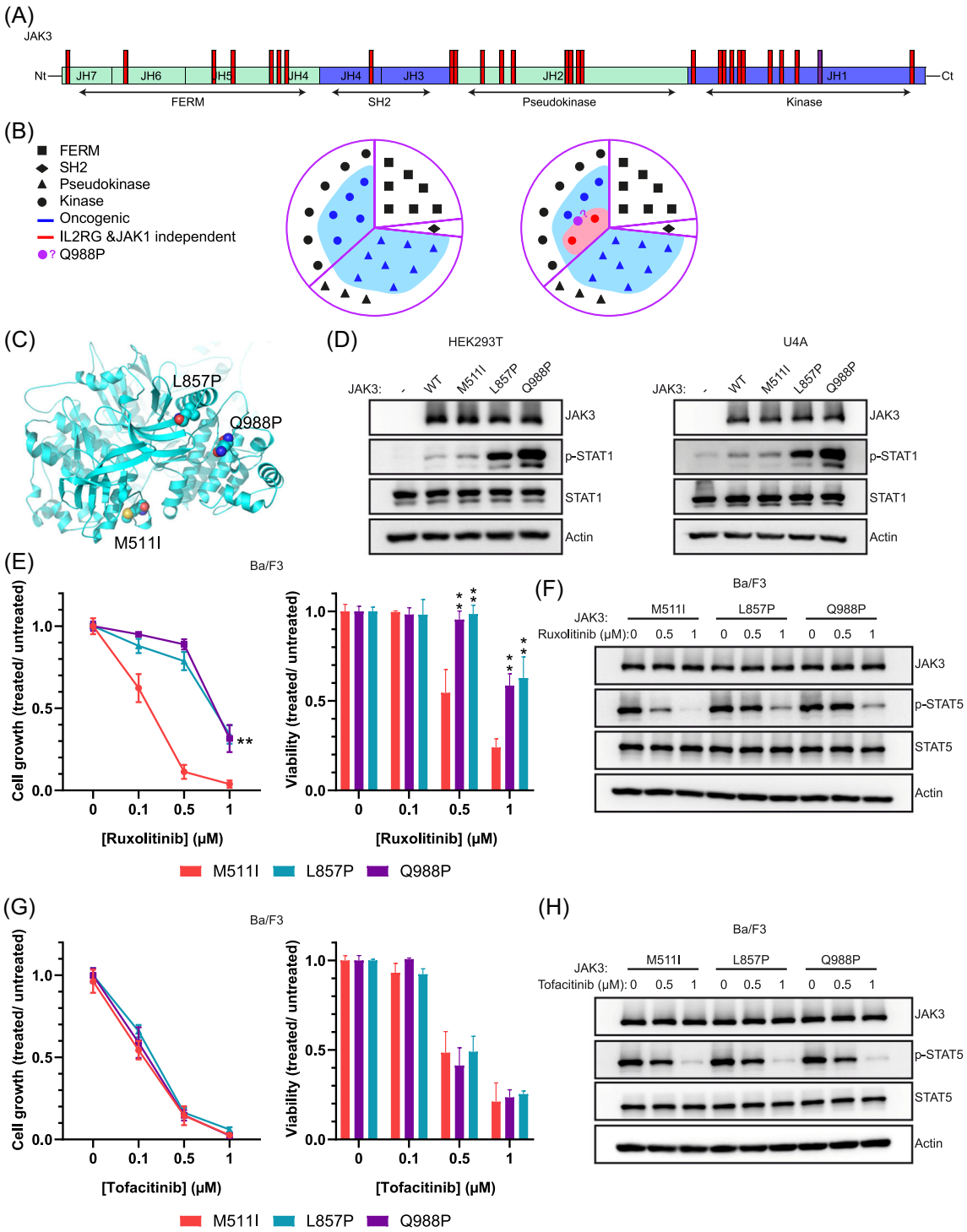

FIGURE 2 (See caption on next page).

ruxolitinib than cells expressing JAK3^{M511I}. Accordingly, STAT5-phosphorylation is less reduced after ruxolitinib treatment in cells expressing JAK3^{Q988P} or JAK3^{L857P} than in cells expressing JAK3^{M511I} (Figure 2F). To confirm that the lower efficacy of ruxolitinib against JAK3^{Q988P} was the consequence of its ability to function independently of JAK1, we treated the different cellular models with tofacitinib, a specific JAK3 inhibitor, which had similar effects on growth, viability and STAT5-phosphorylation (Figure 2G,H). JAK3 mutations have recently been reported to induce apoptosis resistance,[6] so we assessed whether, in addition to pSTAT5, the levels of other proteins implicated in cell survival were also increased in JAK3^{Q988P}-expressing cells compared to JAK3^{M511I}-expressing cells after ruxolitinib treatment. In this respect, we observed that pSTAT1, c-MYC and BCL-XL protein levels were higher in cells transduced with JAK3^{Q988P} than in cells transduced with JAK3^{M511I}, recapitulating the results previously observed for pSTAT5 (Figure S2F). Furthermore, we confirmed that the observed differences derive from an increased resistance of JAK3^{Q988P} to ruxolitinib, since the treatment with tofacitinib elicited similar effects on cells transduced with JAK3^{Q988P} or with JAK3^{M511I} (Figure S2G).

In the present manuscript, we identified the JAK3^{Q988P} mutation in a T-ALL patient at relapse. Although *JAK3* mutations are frequent events in T-ALL, only a limited fraction of them have been functionally characterized as oncogenic. Therefore, addressing the functional consequences of the different *JAK3* mutations following an individualized approach is essential for the development of novel personalized-therapies with greater efficiency and less toxicity. We functionally characterize JAK3^{Q988P} as an oncogenic mutation that contributes to leukemogenesis in hematopoietic cellular models. Specifically, we show that the JAK3^{Q988P} mutation has an oncogenic role and may contribute to leukemogenesis through two different molecular mechanisms. On the one hand, JAK3^{Q988P} promotes constitutive activation of the JAK/STAT pathway in the absence of cytokines and growth factors, which are the canonical inductors of the pathway, similar to what has been reported for most *JAK3* mutations experimentally characterized as oncogenic (such as JAK3^{R549Q}, JAK3^{R887C}, JAK3^{M511I}, JAK3^{A573V}…).[6,8] On the other hand, JAK3^{Q988P} renders the catalytic activity of JAK3 independent of JAK1 and IL2RG proteins, a remarkable feature that has only been described for two other *JAK3* mutations (JAK3^{L857P} and JAK3^{L875H}).[8,16] Therefore, JAK3^{Q988P} promotes increased activation of the JAK/STAT pathway through two molecular mechanisms that are complementary and, together with the JAK3^{L857P} and JAK3^{L875H} mutations, would represent a subset of *JAK3* mutations with higher oncogenic potential than the majority of *JAK3* mutations described in T-ALL. These observations are crucial when proposing personalized-therapies for future patients with JAK3^{Q988P}. Since the JAK3^{WT} protein as well as most oncogenic JAK3 mutants require a functionally active JAK1 protein, previous studies have demonstrated the efficacy of ruxolitinib against multiple *JAK3* mutations.[8,17] In addition, clinical trials and personalized-therapies involving ruxolitinib for the treatment of T-ALL patients with *JAK3* mutations have recently emerged and are delivering promising results.[4,18] However, this may not be the case for patients with JAK3^{Q988P}, as it does not require a functionally active JAK1 protein and has reduced sensitivity to ruxolitinib. In this respect, alternative treatments involving tofacitinib and glucocorticoids may be a more suitable approach for patients with the JAK3^{Q988P} mutation.[6] Overall, our study offers a comprehensive characterization of the JAK3^{Q988P} mutation as a highly oncogenic and potentially treatable alteration in T-ALL.

AUTHOR CONTRIBUTIONS

Antonio Lahera, José Fernández-Piqueras, and María Villa-Morales: conceived the project and the experimental plan. **Antonio Lahera**: designed, performed, and analyzed experiments. **Laura Vela-Martín**: helped with experimental assays and scientific figures preparation. **Pablo Fernández-Navarro**: advised on bioinformatics and statistical analyses. **María Villa-Morales**: analyzed data from TARGET. **Pilar Llamas, José L. López-Lorenzo, and Javier Cornago**: provided clinical care and collected human samples. **Antonio Lahera, José L. López-Lorenzo, José Fernández-Piqueras, and María Villa-Morales**: prepared and wrote the manuscript. **Javier Santos**: assisted with review and editing of the manuscript. All authors approved the manuscript in its final format.

FIGURE 2 JAK3^{Q988P} functions independently of JAK1 and IL2RG and has increased resistance to ruxolitinib treatment. (A) Schematic representation of JAK3 showing the homology regions and protein domains. Mutations identified in T-ALL patients are indicated with red bars. The JAK3^{Q988P} mutation is highlighted in purple. (B) Distribution of *JAK3* mutations identified in T-ALL patients and described in the literature. Mutations functionally characterized as oncogenic are colored in blue. Mutations able to activate the JAK/STAT pathway independently of JAK1 and IL2RG proteins are colored in red. The JAK3^{Q988P} mutation is colored in purple. (C) Bioinformatics model for the structure of JAK3 showing the location of M511I, L857P and Q988P mutants. The structure of JAK3 has been plotted with Pymol. Color legend: carbons in cyan, oxygens in red, nitrogens in blue and sulfurs in yellow. (D) Western blot for JAK3, p-STAT1, and STAT1 in HEK293T (left) and U4A (right) cells untransfected (−) or transfected with JAK3^{WT} or JAK3 mutants. In this case, JAK3^{M511I} and JAK3^{L857P} were used as a negative and a positive control, respectively. (E) Cell growth (left) and viability (right) assays of Ba/F3 cells transduced with JAK3 mutants untreated or treated with ruxolitinib (0.1 μM, 0.5 μM or 1 μM). Data are referred to untreated cells. (F) Western blot for JAK3, p-STAT5, and STAT5 in Ba/F3 cells transduced with JAK3 mutants untreated or treated with ruxolitinib (0.5 μM or 1 μM). (G) Cell growth (left) and viability (right) assays of Ba/F3 cells transduced with JAK3 mutants untreated or treated with tofacitinib (0.1 μM, 0.5 μM or 1 μM). Data are referred to untreated cells. (H) Western blot for JAK3, p-STAT5 and STAT5 in Ba/F3 cells transduced with JAK3 mutants untreated or treated with tofacitinib (0.5 μM or 1 μM). The graphics show the mean ± standard deviation (*SD*) after three independent experiments. *: $p < 0.05$; **: $p < 0.01$. All images are representative examples of at least three independent experiments. T-ALL, T-cell acute lymphoblastic leukemia.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request. Data from the Therapeutically Applicable Research to Generate Effective Treatments (TARGET) initiative are managed by the National Cancer Institute (NCI) and accessible through the genotypes and phenotypes database (dbGaP, https://www.ncbi.nlm.nih.gov/projects/gap/cgi-bin/stud). Additional data that support the findings of this study are available in the supplementary information of this article and/or from the corresponding authors on reasonable request.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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