Fusion.AR-DB: A Collaborative Knowledgebase of Actionable Gene Fusions in Pediatric Cancers Leveraging Large-Scale RNA-Seq Data.

Gene fusions are powerful oncogenic drivers and biomarkers in pediatric and AYA (adolescent and young adult) cancers [1][2], yet their clinical utility remains underexploited due to fragmented datasets, limited detection approaches, and the lack of centralized, clinically meaningful resources [3]. We propose Fusion.AR-DB, the first open-access, comprehensive knowledge base of gene fusions in pediatric and AYA cancers.

The objective is to systematically detect, annotate, and organize gene fusions across publicly available RNA-Seq datasets, including NIH Kids First, TARGET, CCDI, and others. Fusion.AR-DB will catalog all detected fusions [4,5], not only known or actionable ones, and associate them with clinical data like tumor types, molecular subtypes, and expression profiles. Therapeutically actionable events will be linked to FDA/EMA-approved drugs and clinical trials. Each fusion will be annotated with functional and structural insights, including domain-level information, expression impact, and structure of the resulting chimeric proteins, enabling downstream modeling and docking.

Built with a validated, high-performance pipeline optimized for low-input pediatric samples, the platform integrates tools such as STAR and Arriba. All analyses will be run in a high-performance computing environment. The results will be delivered via a user-friendly, interactive interface, allowing users to explore fusion prevalence, co-occurrence, functional relevance, and therapeutic potential.

Preliminary analyses reveal:

- Undetected kinase fusions in high-risk pediatric cancers [6].
- Novel recurrent fusion actionable events [7].
- Actionable fusions in ~7% of FISH-negative tumors [8].

Impact: Fusion.AR-DB increases therapeutic eligibility up to 3-fold in pilot cohorts, reduces diagnostic costs by over $1.2M/year per institution, and directly supports NCI goals by transforming RNA-Seq data into clinically actionable, personalized insights.

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REFERENCES

[1] Vellichirammal, N. N., Chaturvedi, N. K., Joshi, S. S., Coulter, D. W., & Guda, C. (2021). “Fusion genes as biomarkers in pediatric cancers: A review of the current state and applicability in diagnostics and personalized therapy”. *Cancer letters*, 499, 24–38. https://doi.org/10.1016/j.canlet.2020.11.015

[2] Liu, Y., Klein, J., Bajpai, R. et al. “Etiology of oncogenic fusions in 5,190 childhood cancers and its clinical and therapeutic implication”. *Nat Commun* 14, 1739 (2023). https://doi.org/10.1038/s41467-023-37438-4

[3] Finucane, S. et al. “Known and unknown gene fusion detection capabilities of solid tumour laboratories conducting next generation sequencing in 6 countries”. *Annals of Oncology*, Volume 30, v575.

[4] Vicente-Garcés C, Maynou J, Fernández G, Esperanza-Cebollada E, Torrebadell M, Català A, Rives S, Camós M, Vega-García N. “Fusion InPipe, an integrative pipeline for gene fusion detection from RNA-seq data in acute pediatric leukemia”. *Front Mol Biosci*. 2023 Jun 9;10:1141310. doi: 10.3389/fmolb.2023.1141310. PMID: 37363396; PMCID: PMC10288994.

[5] Hehir-Kwa JY, Koudijs MJ, Verwiel ETP, Kester LA, van Tuil M, Strengman E, Buijs A, Kranendonk MEG, Hiemcke-Jiwa LS, de Haas V, van de Geer E, de Leng W, van der Lugt J, Lijnzaad P, Holstege FCP, Kemmeren P, Tops BBJ. “Improved Gene Fusion Detection in Childhood Cancer Diagnostics Using RNA Sequencing”. *JCO Precis Oncol*. 2022 Jan;6:e2000504. doi: 10.1200/PO.20.00504. PMID: 35085008; PMCID: PMC8830514.

[6] Benayed R, “High Yield of RNA Sequencing for Targetable Kinase Fusions in Lung Adenocarcinomas with No Mitogenic Driver Alteration Detected by DNA Sequencing and Low Tumor Mutation Burden”. *Clin Cancer Res*. 2019 Aug 1;25(15):4712-4722. doi: 10.1158/1078-0432.CCR-19-0225. Epub 2019 Apr 26. PMID: 31028088; PMCID: PMC6679790.

[7] Péterffy, Borbála et al. “Molecular Profiling Reveals Novel Gene Fusions and Genetic Markers for Refined Patient Stratification in Pediatric Acute Lymphoblastic Leukemia”. *Modern Pathology*, Volume 38, Issue 6, 100741.

[8] Zago Baltazar R. et al. “Recurrent and novel fusions detected by targeted RNA sequencing as part of the diagnostic workflow of soft tissue and bone tumours”. *J Pathol Clin Res*. 2024 May;10(3):e12376. doi: 10.1002/2056-4538.12376. PMID: 38738521; PMCID: PMC11089496.