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Dissecting genetic and phenotypic heterogeneity to deliver personalized predictions in acute myeloid leukemia patients

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Molecular studies in acute myeloid leukemia (AML) have signposted our understanding of the inter-relationships among mutations, biology, clinical presentation and response to treatment.[1] The characterization of chromosomal abnormalities by cytogenetic methods[2] and their correlation with distinct outcomes has formed the basis of molecular classification in AML.[3-6]

In addition to the recurrent chromosomal aneuploidies, sequencing of AML genomes found 23 significantly mutated genes and ~200 recurrently mutated.[7] Of these, only *NPM1* and *CEBPA* are incorporated as provisional entities into the World Health Organization 2008 classification.[4] Most AML genes are infrequently mutated (<5% of patient population), and AML patients have ≥3 putative cancer gene mutations and are both genetically and clonally heterogeneous.[7-9] Re-sequencing studies uncover specific patterns of co-mutation,[10] many of which carry prognostic significance beyond the established risk groups.[10-11] Large cohort studies of well-annotated clinical specimens matched to molecular profiling provide an opportunity to study genotype-phenotype relationships, how these relate to disease ontogeny in AML[12] and how these inform the development of future clinical algorithms.

Data will be shown from a study of 1,540 AML patients. We explore the presentation of >5,000 driver lesions, use statistical modeling approaches to define molecular ontology and study how these relate to clinical phenotype.[13] Gene mutations and cytogenetic abnormalities delineate 11 classes, each defined by specific patterns of co-mutation, accounting for ~80% of AML. Though each group correlates with clinical phenotype and outcomes, recurrent genotypes within each group associate with additive as well as epistatic effects to overall risk, and account for much of the residual phenotypic and clinical heterogeneity.[13]

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This reference highlights how molecular markers define classification in AML for clinical consideration.

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References 8 and 9 show the importance of molecular markers in defining cell populations associated with diverse clonal dynamics and how these relate to disease progression in AML.

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