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**Analisis variasi genetik herediter mengunakan metode next generation sequencing untuk pencarian kandidat gen faktor risiko kanker paru**
Harvey Romolo, Prof. DR. dr. Ibnu Purwanto, SpPD, KHOM
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# INTISARI

**Latar belakang:** Kanker paru merupakan penyebab kematian akibat keganasan tertinggi di dunia dan di Indonesia. Profil klinis di Indonesia menunjukkan kecenderungan usia pasien yang lebih muda (rerata 55 tahun) dibandingkan populasi dunia barat (rerata 70 tahun). Ketimpangan epidemiologi ini memunculkan dugaan kuat adanya pengaruh variasi genetik herediter (*germline*) yang unik pada populasi Indonesia. Hingga saat ini, data komprehensif mengenai arsitektur varian genetik herediter pada pasien kanker paru di Indonesia masih sangat terbatas.

**Tujuan:** Menganalisis varian mutasi genetik herediter pada pasien kanker paru di Indonesia menggunakan metode *Next Generation Sequencing* (NGS) serta menguji hubungannya dengan faktor risiko guna mengidentifikasi kandidat gen pembawa risiko kanker paru.

**Bahan dan cara kerja:** Penelitian ini menggunakan rancangan kasus-kontrol. Sampel berupa darah tepi yang diambil dari pasien kanker paru (kelompok kasus) dan populasi sehat (kelompok kontrol). Pemeriksaan genetik dilakukan menggunakan metode *targeted* NGS dengan kit komersial *Illumina DNA Prep with Enrichment* dan *TruSight Hereditary Cancer Panel* yang mencakup 113 gen terkait kerentanan kanker. Klasifikasi dan interpretasi varian sekuens dievaluasi lalu dikurasi berdasarkan standar rekomendasi *American College of Medical Genetics and Genomics* (ACMG) menjadi 5 tingkatan.

**Hasil:** Sebanyak 174 pasien kanker paru dan 183 kontrol sehat dianalisis. Pasien didominasi laki-laki (59%), adenokarsinoma (83,9%), dan stadium IV (90,8%), dengan rerata usia 57,1 tahun. Jenis kelamin laki-laki (OR 3,8; 95% CI 2,4–5,8), merokok (OR 9,2; 95% CI 4,9–17,5), dan riwayat kanker keluarga (OR 2,1; 95% CI 1,2–3,7) berhubungan bermakna dengan kanker paru. Kurasi terhadap 2.743 varian menghasilkan 21 varian unik pada 30 pasien (17,2%), yang terdiri atas 1 varian *pathogenic* (MUTYH c.1351G>T pada 2 pasien), 8 varian *likely pathogenic* (ATM, BRCA2, BRIP1, FANCF, NF1, dan RAD50 pada 9 pasien), dan 12 VUS (19 pasien). Varian P/LP pada MUTYH, ATM, BRCA2, NF1, dan RAD50 hanya ditemukan pada kelompok pasien. Profil faktor risiko tidak berbeda bermakna antara pasien pembawa dan bukan pembawa varian.

**Kesimpulan:** Varian germline pada pasien kanker paru di Indonesia terkonsentrasi pada gen jalur perbaikan kerusakan DNA, dengan MUTYH c.1351G>T sebagai kandidat varian risiko yang hanya ditemukan pada pasien. Karena pembawa varian tidak dapat dikenali hanya dari faktor risiko klinis, pemeriksaan genetik germline perlu dipertimbangkan secara lebih luas dan divalidasi pada kohort yang lebih besar sebagai dasar strategi skrining populasi risiko tinggi dan *precision medicine* di Indonesia.

**Kata Kunci:** Kanker Paru, Mutasi Herediter, *Next Generation Sequencing*, *Hereditary Cancer Panel*, Populasi Indonesia.

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# ANALYSIS OF GERM LINE MUTATION OF INDONESIAN LUNG CANCER USING NEXT GENERATION SEQUENCING

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## ABSTRACT

**Background:** Lung cancer remains the leading cause of cancer-related mortality globally and in Indonesia. Clinical data in Indonesia consistently indicates a younger median age at diagnosis (55 years) compared to Western countries (70 years). This epidemiological disparity underscores the hypothesis that unique germline variations may contribute to lung cancer susceptibility within the Indonesian population. To date, comprehensive data maping the architecture of hereditary genetic variants in Indonesian lung cancer patients remains severely limited.
**Objective:** To analyze hereditary genetic mutation variants in Indonesian lung cancer patients using Next-Generation Sequencing (NGS) and to evaluate their association with risk factors to identify candidate susceptibility genes.
**Materials and Methods:** This study employs a case-control design. Peripheral blood samples are collected from lung cancer patients (case group) and healthy individuals (control group). Genetic analysis is conducted via targeted NGS utilizing the commercial *Illumina DNA Prep with Enrichment* kit and the *TruSight Hereditary Cancer Panel*, targeting 113 cancer-predisposition genes. Sequence variants are classified and interpreted based on the 5-tier recommendation standard of the American College of Medical Genetics and Genomics (ACMG).
**Results:** A total of 174 lung cancer patients and 183 healthy controls were analysed. Patients were predominantly male (59%), had adenocarcinoma (83.9%), and stage IV disease (90.8%), with a mean age of 57.1 years. Male sex (OR 3.8; 95% CI 2.4–5.8), smoking (OR 9.2; 95% CI 4.9–17.5), and family history of cancer (OR 2.1; 95% CI 1.2–3.7) were significantly associated with lung cancer. Curation of 2,743 variants yielded 21 unique variants in 30 patients (17.2%): 1 pathogenic variant (MUTYH c.1351G>T in 2 patients), 8 likely pathogenic variants (ATM, BRCA2, BRIP1, FANCF, NF1, and RAD50 in 9 patients), and 12 VUS (19 patients). P/LP variants in MUTYH, ATM, BRCA2, NF1, and RAD50 were found only in patients. Risk factor profiles did not differ significantly between carriers and non-carriers.

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**Conclusion:** Germline variants in Indonesian lung cancer patients cluster in DNA damage repair genes, with MUTYH c.1351G>T emerging as a candidate risk variant found only in patients. Because carriers cannot be identified from clinical risk factors alone, broader germline testing should be considered and validated in larger cohorts to inform high-risk screening strategies and *precision medicine* in Indonesia.

**Keywords:** Lung Cancer, Germline Mutation, Next-Generation Sequencing, Hereditary Cancer Panel, Indonesian Population.