Universitas Indonesia Library >> UI - Disertasi Open

Faktor-faktor genetik pengubah manifestasi klinis thalassemia interaksi antara mutasi thalassemia polimorfisme dan SNPs pada klaster gen globin

Pustika Amalia Wahidiyat, author

Deskripsi Lengkap: https://lib.ui.ac.id/detail?id=20377731&lokasi=lokal

---

Abstrak

Latar belakang: Thalassemia dan hemoglobinopati merupakan kelainan gen tunggal terbanyak di dunia, termasuk di Indonesia dengan frekuensi pembawa sifat thalassemia-~ 3-10% dan HbE 1-36%. Thalassemia-WIThE adalah bentuk heterozigot ganda paling sering ditemukan dengan gejala klinis bervariasi, dari asimtomatik sampai berat. Beberapa faktor pemodifikasi telah diketahui memengaruhi manifestasi klinis. Faktanya pasien dengan jenis mutasi sarna dapat memiliki manifestasi klinis berbeda. Hal itu menunjukkan ada faktor pemodifikasi lain yang memengaruhi derajat manifestasi klinis. Tujuan: Meneari faktor-faktor genetik yang memengaruhi manifestasi klinis, antara lain MGP: bg2, bgll dan bg 200 yang diduga berhubungan dengan meningkatnya produksi HbF dan memengaruhi variasi manifestasi klinis. Metode penelitian: Penelitian dilakukan dengan metode belah lintang pada pasien thalassemia-~IHbE yang berobat ke Divisi Hematologi-Onkologi Dept. IKA dan Dept. IPD, RSCM, Lembaga Biomolekular Eijkman Jakarta, serta rumah sakit lain sejak bulan Desember 2006 sampai dengan Oktober 2008. Tahap I mendapatkan 293 subjek, terdiri atas 63 subjek ringan (skor <4), 101 subjek intermedia (skor 4-7,5), dan 129 subjek herat (skor ~7,5). Seluruh subjek menjalani pemeriksaan hematologi termasuk indeks eritrosit, morfologi eritrosit, analisis Hb dan feritin serum. Tahap IT dilakukan pemeriksaan jenis mutasi thalassemia-~, termasuk delesi besar gen globin-~ (HPFH tipe delesi), dan jenis mutasi thalassemia-a (co-inheritance dengan thalassemia-a dan triplikasi rantai globin-a) pada 192 subjek kelompok ringan dan berat. Tahap m dilakukan pemeriksaan HPFH nondelesi (polimorfismeXmnI-Gy) dan SNPs: bg2, bg11 dan bg200 pada 187 subjek kelompok ringan dan berat dengan mutasi-~o dan _~+beJat mumi. Pemeriksaan SNPs dilakukan dengan teknik RDB dan teknik sekuensing langsung. Basil penelitian dan pembabasan: Hasil penelitian menunjukkan jenis mutasi thalassemia-~ bukan faktor yang memengaruhi manifestasi klinis, kecuali mutasi IVS 1- nt5 (jenis mutasi-~+bera~ yang berhubungan dengan manifestasi klinis berat (P<0,05). Delesi satu gen globin-a (3.7 kb) berhubungan dengan manifestasi klinis ringan, sedangkan polimorfisme XmnI-G'Y tidak memengaruhi manifestasi klinis. Dari 3 buah SNPs, hanya bg200 yang berhubungan dengan manifestasi klinis (RR: 4,15 (1,22 < RR < 14,17) danp<O,05). Subjek dengan polimorfisme CC pada bg200 memiliki peluang 4,15 kali bermanifestasi klinis berat. Kesimpulan: Penelitian ini menunjukkan beberapa faktor pemodifikasi dapat memengaruhi derajat penyakit pasien thalassemia-~IHbE di Indonesia. Penelitian ini juga menunjukkan belum adanya keseragaman tata laksana thalassemia di Indonesia. Usia pertama diagnosis ditegaklcan, rerata Hb pra-transfusi, frekuensi kebutuhan transfusi, dan ukuran limpa memengaruhi manifestasi klinis sebesar 74% (regresi linear p<0,05).

.....Background: Thalassemia and hemoglobinopathy are the most common monogenic diseases in the world including Indonesia, with gene frequencies of ~-thalassemia 3-10% and for HbE 1-36%. Compund heterozygote ~-thalassemialHbE is one of the world's most common form, have a wide variation of clinical manifestations ranging from asymptomatic to transfusion-dependent. Several major modified genetic factors (MGP) which can influence the phenotype have been reported. The fact that patients with identical p-

thalassemia mutations showed different clinical severity. This finding suggests that there are other MGP which contribute to the severity of the diseases. Purpose: To fmd ·several modifying gene factors including SNPs: bg2, bgll and bg200 which had tendency to increase HbF production and influences the clinical manifestations of p-thalassemialHbE. Materials and Methods: This was a cross sectional study to a total 293 subjects with pthalassemia/ HbE patients from Department of Child Health and Department of Internal Medicine, Cipto Mangunkusumo National Hospital, Eijkman Institute for Molecular Biology, Jakarta and other hospitals from December 2006 until October 2008. Phase I: Subjects were divided into mild (score <4, n=63), intermediate (score 4-7.S, n=101), and severe (score 2: 7.S, n= 129) using Thailand severity scoring. Hematological parameters including CBC, red cell indices and morphology, Hb analysis and serum ferritin were performed. Phase ll: 192 subj ects from mild and severe group were performed to characterize the ~thalassemia mutation, including large deletion of P-globin gene (deletion HPFH) and interaction of 0.thalassemia (deletion, non deletion a-thalassemia and a-globin gene triplication). Phase ill: XmnI-Gy polymorphisms and 3 SNPs: bg2, bgll and bg200 executed from 187 subjects of mild and severe groups with ~o - and ~~ -thalassemia mutation without any gene interaction. SNPs were performed by RDB and direct sequencing. Results: In this study types of p-thalassemia mutation are not the modifying factor contribute to the Clinical manifestation, except the · IVS I-ntS that correlate with severe clinical manifestations (p<O.OS). One gene deletion <?7 kb) of a-thalassemia had contributed to milder clinical manifestation, while XmnI- y polymorphisms not related to clinical manifestation. From the 3 SNPs, only bg200 related to clinical manifestation (RR: 4.1S (1.22<RR<14.17), p<O.OS). Subjects with polymorphism CC in bg200 have a tendency 4.1S times to become severe clinical manifestation. Conclusions: This study showed that there are several modifying factors which modulate the clinical severity of p-thalassemialHbE patients in Indonesia. This study also showed that the management of thalassemia in Indonesia has not been optimal resulted in the unspesific clinical severity. Clinical manifestation was 74% influenced by age at diagnosis, Hb at steady state, frequency of transfusion and spleen size (p<O.OS).