Bölüm 13

İNTERLÖKİN (IL)-10 GENİNİN -1082 (G/A), -819 (C/T), -592 (C/A) PROMOTOR POLİMORFİZMLERİ VE İLİŞKİLİ PATOLOJİLER

Sibel ÖZDAŞ[1]

GENETİK POLİMORFİZM

Belirli bir türün farklı bireyleri genetik olarak birbirinin aynı değildir. DNA dizileri bir dereceye kadar farklılık gösterir ve bu farklılıklar bir türün bilinen genetik çeşitliliğin temelini oluşturur (Lewontin vd., 1966; Harris vd., 1966). Bu DNA dizi varyasyonları beslenme ve üreme stratejileri, geliş bulaşıcı hastalıkların yönetimi gibi yeni özellikler kazandırarak bir türün adaptasyon kapasitesini artırır, bu nedenle gen ve genom dizileri, biyolojik evrime yön vermiştir (Vander vd., 2012; Forcada ve Hoffman, 2014 Hake ve Ross-Ibarra, 2015; Soares ve Weiss, 2015).

Bir kromozomun spesifik bir lokusunda buluan DNA dizi alternatiflerine "alel" denir. İnsan otozomal kromozomunun her bir lokusunda anne ve babadan gelen iki allel bulunur ve belirgin bir karakterin genetik bilgisini temsil eder. Popülasyonlarda bir allelin bulunma sıklığı değişken olup, populasyonun tüm genlerine ait allel frekansları karakterize edillebilir (Basaran N. 1999). İnsan genomunun yaklaşık %0.1'i allelik varyasyon göstermekte olup, bu varyasyonların kaynağı sıklıkla polimorfizmler olmakla birlikte, insersiyon, delesyon gibi mutasyonlar ve rekombinasyonla da olabilir (Cooper vd., 1985). Varyasyonlar her zaman fenotipe yansımasa da bir kısmı işlevsel öneme sahip olup, anatomik-fizyolojik-metabolik farklılıklar, hastalıklara karşı koruyuculuk, hastalıklara yatkınlık, hastalıkların ilerlemesi, terapötik yanıt, ilaç direnci, istenmeyen ilaç reaksiyonları ve karakter özellikleri gibi insanlar arasında bulunan çeşitliliğin temelidir (Collins vd., 1997; Quintana-Murci ve Clark, 2013; Bodmer, 2015).

Polimorfizmler soyların takibinde kromozomal kalıtım paterni olarak kullanılabileceği gibi insan hastalıklarıyla ilişkili genetik faktörlerin araştırılmasında önemli araçlardır (Johnson ve Todd, 2000; Risch, 2000). DNA'yı enzimatik

[1] Dr. Öğr. Üyesi, Adana Alparslan Türkeş Bilim ve Teknoloji Üniversitesi, Mühendislik Fakültesi, Biyomühendislik Bölümü, Genetik ve Moleküler Mühendisliği ABD, Adana, Türkiye, e-mail: sozdas@atu.edu.tr

SONUÇ VE ÖNERİLER

İnsan genomunun yaklaşık %0.1'i allelik varyasyon göstermekte olup, bu varyasyonların kaynağı özellikle SNP polimorfizmlerdir. Bir antienflamatuvar sitokin IL-10, immün cevabın düzenlenmesinde kritik rol oynadığından, yapılan çalışmalar birçok patolojinin moleküler mekanizmasına katkısı olan önemli bir aday gen olduğunu göstermiştir. *IL10* geni polimorfik olmasına rağmen özellikle promotör bölgesindeki -1082, -819, -592 SNP'lerinin genin ifade düzeyini manüple ederek, ürün miktarını değiştirebileceği gösterilmiştir. *lL-10* 1082, -819, -592 SNP allel, genotip ve haplotip dağılımlarının popülasyonlar arasında farklı olduğu gözlenmiştir. Yapılan çalışmalarda *IL-10* -1082G allelinin yüksek ifade düzeyine neden olarak, erken doğum, sistemik lupus eritematozus, tüberküloz, astım riski akciğer kanseri, lenfoma, nazofarengeal, prostat, servikal ve baş boyun kanseri gibi patolojiler için riski arttırdığı bildirilmiştir. Bununla birlikte *IL-10* -819C alelinin sistemik lupus eritematozus, tüberküloz enflamatuvar bağırsak hastalığı ve küçük hücreli olmayan akciğer kanseri, -592A allelinin ise obstrüktif uyku apnesi ve nazal polipozis riskini artırdığı raportlanmıştır. Düşük IL-10 düzeyi ile ilişkili *IL-10* -1082AA, -592AC, -592AA genotipleri astım, obstrüktif uyku apne, -819TT ve -592AA genotipleri ise prostat ve kolon kanseri riskiyle ilişkilidir. Düşük IL-10 üretimine neden *IL-10* ATA haplotipinin astıma, psoriasise, obstrüktif uyku apnesine, melanomaya yatkınlıktan sorumlu olduğu ve hastalığın siddetinde belirleyici rol oynadığı gösterilmiştir. Buna rağmen artmış IL-10 üretimi *IL-10* GCC haplotipinin frekansı prostat kanseri ve sistemik lupus eritematozuslu hastalarda kontrole kıyasla yüksektir. IL-10'nun artan veya azalan düzeyinin patolojik bir önemi olup, *IL-10* gen polimorfizmlerinin patolojilerle ilişkisini ve hastalık patogenezindeki fonksiyonunu anlamak için ileri düzey çalışmalara ihtiyaç vardır.

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