Bölüm
41

NÖROGENETİK HASTALIKLAR

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GİRİŞ

Nörogenetik son yıllarda hızla gelişmekte olan bir alandır. Genel popülasyonun %1'inden fazlasında çeşitli kromozom varyantları bulunmaktadır. Bu genetik varyantlar pek çok nörolojik hastalığın gelişiminden sorumlu tutulmaktadır. Genetik alanında yeni gelişmeler sonucu tespit edilen birçok spesifik genlerin nörolojik hastalıkların %80'inden fazlasında etiyolojide sorumlu tutulduğu bilinmektedir. Genetik alanındaki son gelişmeler bireyin genetik dizisini belirleyip buna uygun tedavi stratejileri ortaya çıkarmak ve tedavisi zor olan nadir hastalıkların tedavisinde ilerleme sağlamayı amaçlamaktadır. Bu çalışmada amacımız nörogenetik hastalıkların sınıflandırılması ve genetik varyasyonlarının ortaya konulması ile ilgili bilgileri yeniden gözden geçirmektir.

FDA (Food and Drug Adminisration) tarafından tanımlanan verilere göre ABD (Amerika Birleşik Devletleri) 'inde 200.000'den az, Avrupa'da ise 5/10000 sayıda insanı etkileyen ve sıklıkla genetik geçişli olan nadir hastalıklar tespit edilmiştir. Bu hastalıkların sayısı yaklaşık 6000 civarında olup dünya nüfusunun %6-10'unu etkilemektedir (1).

25 milyon civarında Amerikan vatandaşı ve 10 milyon civarında da Çin vatandaşı, nadir hastalıklardan etkilenmiştir. Söz konusu nadir hastalıkların %80'i genetik geçişli olup bir kısmı tek gen diğer bir bölümü de çoklu gen mutasyonlarına bağlı gelişmektedirler (2,3).

İnsan genomu 23 çift kromozomdan oluşmaktadır ve bunun 22'si otozom hücrelerden diğer bir kromozom da gonozom hücrelerden olmak üzere toplam 46 kromozomdan oluşmaktadır (4,5). Bu kromozomlar ortalama 80-300 bin baz çiftinden meydana gelmektedirler. Her bir kromozom kendi özdeş kromozomu ile karşı karşıya gelerek büyükten küçüğe doğru sıralanmakta ve "karyotip" olarak isimlendirilir. Kromozomlar içerisinde DNA'lar, DNA'lar içerisinde de genler yer almaktadırlar. DNA ise genetik materyaldir ve DNA (Deoksiribo Nükleik Asit) nükleotidlerin karşı karşıya gelmesi sonucu iki iplikten oluşan çift sarmallı bir yapıdadır. Nükleotidler; bir fosfat grubu, bir azotlu baz (Adenin, Timin, Guanin ve Sitozin gibi) ve bir pentoz (5 Karbonlu şekerden) oluşur. Adenin ve Guanin pürin bazı, Timin ve Sitozin pirimidin bazlarıdır. Adenin bazının karşısında Timin, Guanin bazının karşısına ise Sitozin gelmektedir. DNA'da saklanan genetik bilgilerin, RNA'ya aktarılmasına ''Transkripsiyon" denir. Transkripsiyon ile RNA'ya kopyalanan genetik bilgilerin bir protein molekülü haline çevrilmesine de "Translasyon" denir. Bu olayların tamamı gen ekspresyonu olarak ifade edilir (6,7).

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mu 12p11.2-q13.1 kromozomundaki *LRRK2* genindeki mutasyonlara bağlı PARK8›dir (106,107).

LRRK2'nin en sık mutasyonu olan G2019S bulguları idiyopatik parkinsonizme benzer bulgular göstermektedir(108,109).

Parkin (PARK2) gen mutasyonları, otozomal resesif kalıtım gösterir. Hastalık semptomları 50 yaşından önce başlar ve de distoni ve postural instabilite çok daha erken görülmektedir(110,111).

Mitokondriyal PTEN aracılı Kinaz 1 geninin (PINK1,PARK6) mutasyonları da otozomal resesif geçişlidir (112,113).

Mitokondriyal *DJ-1* geninin (*PARK7*) mutasyonları, otozomal resesif kalıtım paternine uymaktadır(114,115). Tüm bu gen mutasyonları Parkinson hastalığı ile ilişkili başlıca genetik faktörler arasında yer almaktadırlar.

MİGREN

Migren episodik, şiddetli başağrıları ile karakterize yaygın sık görülen ve işlevselliği etkileyen en sık görülen nörolojik hastalıklardan biridir (116,117).

Trigeminal afferentlerin uyarılması ve inflamatuar maddelerin salınımı sonucunda, vazodilatasyon ve ağrı meydana gelir. Aile öyküsü bulunanlarda 2-3 kat daha sık görülmektedir (43,45).

Familyal hemiplejik migren (FHM)'de, motor güçsüzlük ve sık auralı migren atakları görülür. CACNA1A (Kalsiyum kanalı), ATP1A2 (Sodyum-potasyum ATP pompası) ve SCN1A (Sodyum kanalı) iyon kanallarında otozomal dominant mutasyon ile karakterizedir (118,119).

NOTCH3 geninde mutasyon sonucu gelişen vasküler değişiklikler, demans, migren ve enfarkt görülen tablo CADASIL olarak adlandırılmaktadır (120).

SONUÇ

Nörogenetik tıpta hızlı gelişmekte ve gelecekte umut vaat etmektedir. Gelişmekte olan pek çok genetik testlerle monogenik ve poligenik birçok genetik hastalığın tanısını koyma konusunda önemli aşamalar kaydedilmiştir. Spinal müsküler atrofi gibi birçok hastalığın tedavisinde de önemli gelişmeler tespit edilmiştir. Bununla birlikte nörogenetik alanında gelecekte de pek çok genetik hastalığın tanı ve tedavisinde ilerlemeler sağlanacağı konusunda, çok merkezli çalışmaların devam edeceğini ve yeni hedefler göstermesini bekliyoruz.

Anahtar Kelimeler: Nöro-genetik, otozomal dominant, otozomal resesif, X'e bağlı geçiş

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