yanında bu rahatsızlıkların tedavisinde kullanılan yöntemlere verilen yanıtı da etkileyebilmektedir. Özellikle strese karşı verilen tepkileri düzenlemede etkili genlerde görülen tek nükleotid polimorfizmlerinin tedavi etkinliği ile ilişkili olabildiği önerilmiştir. Örneğin, *CRHR1* geni üzerindeki tek nükleotid polimorfizmlerinin (rs1876828, rs1876828 ve rs242941) antidepresanların depresyon üzerindeki etkisini artırabildiği gözlenmiştir (Liu ve ark., 2007). Bulgular, rs242941 polimorfizmi için G alelinin ve üç polimorfizm için GAG haplotipinin yüksek kaygı belirtileri olan depresyon hastalarında antidepresan tedavisine olumlu yanıtla ilişkili olduğunu göstermiştir (Liu ve ark., 2007). Gen-çevre etkileşimindeki dinamik yaklaşıma paralel olarak, epigenetik süreçlerin de psikiyatrik problemlere yönelik müdahalelerin etkinliği ile ilişkili olduğunu gösteren çalışmalar hızla artmaktadır. Özellikle DNA metilasyonuyla ilgili bulgular, stres tepkisinde rol alan genler üzerindeki DNA metilasyon düzeylerinin çeşitli tedavi tekniklerine verilen yanıtla ilişkili olabileceğini göstermiştir (Kumsta, 2019).

Kan örnekleri üzerindeki analizler sonucu stres tepkisiyle ilgili süreçlerde rolü olan genler üzerindeki DNA metilasyon farklılıklarının aktif ilaç tedavilerine verilen yanıt ile ilişkili olduğu düşünülmektedir. Örneğin, *SLC6A4* geni üzerindeki DNA metilasyonunun ilaç tedavisi alan depresyon hastalarında daha yüksek olduğu ve hatta ilaç kullanmayan hastalarla sağlıklı kontrol grubu arasında anlamlı farklılıkların olmadığı rapor edilmiştir (Carlberg ve ark., 2014). İlaç tedavisine yönelik daha detaylı bir çalışma, depresyonlu hastalarda *SLC6A4* geninin promotör bölgesindeki belli DNA metilasyon farklılıklarının seçici serotonin geri alım inhibitörleri (SSRI) kullanan depresyon hastalarında ilaç kullanmayan ya da dual antidepresanlarla tedavi edilen hastalara göre daha yüksek düzeyde olabildiğini göstermiştir. Çalışmada, SSRI etkisinin cinsiyet, yaş, çocukluk travmaları veya hipokampal hacimden bağımsız olarak yüksek DNA metilasyon düzeyiyle ilişkili olduğu gözlenmiştir (Booij ve ark., 2015). Bipolar bozukluk tanısı olan hastalarda duygudurum düzenleyici ilaçlara ek olarak antidepresan kullanımının *BDNF* geni üzerinde daha yüksek düzeyde DNA metilasyonuyla ilişkili olduğu rapor edilmiştir. Buna ek olarak, lityum ve valproat kullananlarda diğer ilaçları kullanan hastalara göre daha düşük düzeyde DNA metilasyonu gözlenmiştir (D'Addario ve ark., 2012). Duygudurum düzenleyici ilaçlarla beraber alınan antidepresan tedavisine ait benzer bulgular depresyon hastalarında da kaydedilmiştir (D'Addario ve ark., 2013).

Terapötik müdahaleler de çevresel ajanlar olarak stresle ilgili epigenetik mekanizmalarla ilişki içinde görünmektedir. TSSB'den mustarip savaş gazileri üzerinde yürütülen bir çalışmada, Yehuda ve arkadaşları (2013), HPA aksının işleyişinden sorumlu *FKBP5* geni üzerinde terapiye bağlı DNA metilasyon farklılıkları tespit etmiştir. Çalışmada, kandan alınan örnekler üzerindeki incelemelerde promotör bölgedeki DNA metilasyonunun uzun süreli maruz bırakma terapisinin başarılı olduğu grupta azalmış, ilerleme kaydedilemeyen grupta ise artmış olduğu gözlenmiştir. Bunun yanı sıra, stres düzenlemede önemli bir gen olan *NR3C1* geni promotör bölgedeki terapi öncesi yüksek düzeyde olan DNA metilasyonunun terapi sonrasında TSSB belirti düzeyinde azalmayla ilişkili olduğu görülmüştür. *FKBP5* geniyle ilgili benzer bulgular kaygı bozukluğu için de tespit edilmiştir. Kaygı bozukluğu olan çocuklardan daha önce erken olumsuz yaşantılarla ilişkili bulunan *FKBP5* risk alelleri taşıyan grupta bilişsel davranışçı terapi sonrası azalmış DNA metilasyonu ile azalmış anksiyete belirtileri arasında anlamlı ilişki tespit edilmiştir (Roberts ve ark., 2015). Aynı grupta altı aylık takipte tedaviye olumlu yanıt veren çocuklarda yanak içi doku ve tükürükten alınan örneklerde *SLC6A4* geni promotör bölge üzerinde DNA metilasyon artışı gözlenmiş, tedaviye yanıt vermeyen grupta ise aynı gen üzerindeki metilasyon derecesinde azalma kaydedilmiştir (Roberts ve ark., 2014, 2015). Sınırda kişilik bozukluğu tanısı almış kişilerle yürütülen diyalektik davranış terapisinin *BDNF* genindeki metilasyon derecesiyle ilişkili olduğu bulunmuştur. Sınırda kişilik bozukluğu olan kişilerin kanlarından alınan örnekler incelendiğinde *BDNF* genindeki metilasyon düzeyi terapiye yanıt vermeyen grupta artarken olumlu yanıt verenlerde azalmıştır (Perroud ve ark., 2013).

Stresle ilişkili genlerdeki tek nükleotid polimorfizmlerinin ve DNA metilasyonlarının psikopatolojilere müdahale teknikleriyle olan ilişkileri ilgili mekanizmaları aydınlatıcı bilgiler taşımaktadır. Bulgular, psikiyatrik problemlerle mücadelede gerek ilaçlar gerekse çeşitli psikoterapi tekniklerinin stres yönetim mekanizmalarına etki ederek fayda sağlıyor olabileceğini göstermektedir. Bu durum, ayrıca, neden bazı hastaların belirli müdahale tekniklerinden fayda görürken bazılarının göremediğini de açıklıyor olabilir. Olumlu çevresel ajanlar olarak düşünüldüğünde söz konusu müdahalelerin etki mekanizmaları ve diğer genetik ve/veya çevresel faktörlerle etkileşimlerine yönelik kapsamlı çalışmalara ihtiyaç vardır.

Sınırlılıklar ve öneriler

Psikiyatrik rahatsızlıkların genetik ve epigenetik süreçlerle olan ilişkileri biyolojik mekanizmanın çevresel yaşantılarla etkileşim içinde olduğunu göstermektedir. Bu alanda yürütülen çalışmalar oldukça hassas ve masraflı olmanın yanı sıra birtakım teknik kısıtlılıklar içermektedir. Çalışma bulguları değerlendirilirken söz

konusu kısıtlılıkların göz önünde bulundurulması ve farklı yöntemlerle yürütülen çeşitli örneklemlerde tekrarlanması önerilmektedir.

Hedef genlere odaklanan çalışma teknikleri tüm genom/epigenoma yayılanlara kıyasla istatistiksel güç açısından daha avantajlı olarak değerlendirilmektedir. Özellikle, psikopatolojiler ve ilgili çevresel yaşantılarla olan etkileşim bağlamında düşünüldüğünde klinik deneyimler sonucu öngörülen mekanizmaları yöneten genlere odaklanılarak yeterli istatistiksel verimlilikle öngörülen etkiler incelenebilmektedir. Bununla beraber, tüm genom/epigenoma yayılan çalışmalar yeni genlerin ve genler arasındaki ilişkilerin ortaya çıkarılması bakımından düşük istatistiksel güce rağmen tercih edilebilmektedir (Amos ve ark., 2011; Moore, 2017). Ancak, psikopatolojilerin genellikle çoklu ve ortak genetik varyanslarla ilişkili olduğuna yönelik bulgular genetik ilişkilendirme çalışmalarının psikopatolojileri anlamadaki kısıtlılıklarını göz önünde bulundurmayı gerektirmektedir (Smoller ve ark., 2019).

Epigenetik ve zihin sağlığı araştırmalarının karşılaştıkları önemli kısıtlılıklardan biri, beyin dokusuyla çalışmanın her zaman mümkün olmamasıdır. İnsan vücudunda her hücrede aynı DNA dizilimi olmasına rağmen epigenetik mekanizmalar sonucu söz konusu genetik materyal birbirinden çok farklı hücre tiplerini oluşturabilmektedir. Zihin sağlığı alanında hedef organın beyin olması beyin hücreleri üzerinde çalışmayı gerektirmektedir. İnsanda beyin hücreleri üzerinde ölüm sonrası çalışmalar mevcut olsa da kan ya da ağız içi salgılardan alınan örnekler kadar yaygın çalışılması mümkün değildir. Beyinle ilgili çalışmalarda kan örnekleri üzerinde yürütülen çalışmaların faydalı olup olmadığına dair tartışmalar devam etmektedir (Bakulski ve ark., 2016; Hannon ve ark., 2015). Çalışmalarda genellikle çevresel hücrelerdeki DNA metilasyonlarına bakıldığından bu değişimlerin sinir hücrelerinde nöral aktiviteye bağlı DNA metilasyon profilini ne kadar paralel olarak yansıttığı sorunsalı dikkate alınmalı ve bulgular olası biyolojik işaretler olarak değerlendirilmelidir (Hannon ve ark., 2015).

Bir diğer kısıtlılık ilişkisel çalışmaların çoğunda karşılaşılan nedensellik çıkarımının yapılamamasıdır. Örneğin, DNA metilasyonu ile psikopatolojiler arasındaki anlamlı ilişki, metilasyonun problemlere yatkınlığı belirliyor olması kadar patolojiye bağlı metilasyon değişimlerine de işaret ediyor olabilir. Bu sebeple çalışma bulguları dikkatli değerlendirilmeli ve boylamsal çalışmalarla desteklenmelidir. Çalışmalarda kontrol grubunun dahil edilmesi DNA metilasyonunda zamanla görülebilen stokastik dalgalanmaların karıştırıcı etkisini kontrol edebilmek bakımından oldukça önemlidir. DNA metilasyonlarında genelde küçük değişimler görüldüğünden yeterli hassasiyete sahip tekniklerin kullanılması gerekmektedir (Kumsta, 2019).

Son olarak, psikiyatrik rahatsızlıklarda genetik ve epigenetik etkilerin incelenmesinde değerli çalışmalar olan ikiz çalışmalarında ikizlerin tek ya da çift yumurta olduklarının güvenilir bir biçimde tespit edilmesi bulguların doğru yorumlanmasında kritik öneme sahiptir. Bu nedenle, ikiz çalışmalarında eşlerin tek ya da çift yumurta ikizi olup olmadıkları analiz protokolünün bir parçası olarak yer almalıdır (Machin, 2009). Ayrıca, psikiyatrik problemler açısından farklılık gösteren ikiz eşleriyle çalışılırken, fenotipik farklılığın iyi araştırılması gerekmektedir. Benzer epigenetik mekanizmaların etkili olduğu problemlerde ikiz eşlerinin farklı tanılar altında değerlendirilmesi epigenetik profilde örtüşmelere yol açabilir. Bu çalışmalarda hastalığın başlangıç yaşının araştırma zamanına çok yakın olmaması önerilmektedir. Bunun sebebi, diğer ikiz eşinin de kısa zaman içinde aynı hastalık tanısını almasının olası bir durum olması ve fenotipik farklılığın gerçekliğinin doğrulanmasına duyulan ihtiyaçtır (Kato ve ark., 2005).

Sonuç

Genetik ve epigenetik mekanizmalar çevresel etkilerin genomik fonksiyonlarımızda değişimlere yol açabildiğini göstermektedir. Özellikle stresle ilgili genleri hedef alan çalışmaların bulguları, stresli yaşantıların patolojiye dönüşmesindeki biyolojik süreçlerin daha iyi anlaşılmasına katkı sağlamaktadır. Bulgular, ayrıca, bazı bireylerde psikolojik problemlere karşı dirençlilik ya da bazı hastalarda tedaviye olumlu yanıt mekanizmalarını anlamayı kolaylaştırmaktadır. Genomik fonksiyonların önemine işaret eden epigenetik mekanizmalarla beraber gen-çevre etkileşimine yönelik bulgular, patolojilerin etiyolojilerini daha iyi anlamayı ve onlara etkin müdahale yöntemleri ile yaklaşmayı mümkün hale getirebilir. Ayrıca söz konusu bilgiler ilgili risk gruplarının belirlenmesi ve önleyici müdahale programlarının geliştirilmesi gibi alanlarda da oldukça faydalı olabilir. Böylece hem patolojilere yol açan hem de baş etmeye yardımcı olan süreçler hakkında farklı ekollerin katkıları ortak bir dil kullanılarak tanımlanabilir ve kullanılabilir.

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| Extended Abstract |
Gene-environment interaction in psychopathologies: Stress-related genetic and epigenetic influences

Esra Zıvralı Yarar[1]

Keywords
psychopathology, stress, gene-environment interaction, epigenetics

Abstract
It has long been known that stressful life events are related to various psychological problems. The relationship between stress and psychiatric disorders has been further recognized due to reports of studies investigating interactions between biological and environmental factors. This paper is about the effect of stress-related environmental factors on psychopathologies through relevant biological mechanisms, such as genetic and epigenetic processes, in human body. Single-nucleotide polymorphisms and DNA methylation profiles of the genes playing role in the autonomic nervous system and the hypothalamic-pituitary-adrenal axis, which are essential for mental health and stress regulation, shed light upon gene-environment interactions in psychopathologies. Research results showing an association between early/late adversities and psychiatric problems through biological mechanisms deserve note. Relationships between genes related to stress regulation, such as *CRHR1*, *FKBP5*, *CRHBP*, *SLC6A4*, *NR3C1*, *OXTR* and *BDNF*, and various psychiatric conditions (e.g., depression, suicide, anxiety, bipolar disorder, personality disorders and post-traumatic stress disorder) have been suggested in an interaction with environmental factors. The number of studies reporting similar associations for therapeutic approaches to these disorders is also on the increase. Possible limitations when interpreting findings and suggestions for future research have also been discussed.

Individual differences have been reported in the effects of stressful life events on psychological health. Studies have reported significant associations between early stressful life events and psychopathologies (e.g., schizophrenia and depression) later in life (Hackman et al., 2010; Mann & Currier, 2010; Turecki et al., 2012). Genetic and epigenetic research highlights possible mechanisms of the interplay between biological and environmental effects explaining the etiology of and treatment approaches to psychopathologies. This paper aimed to present findings on the relationship between adverse life events and psychopathologies through genetic/epigenetic mechanisms (i.e., single nucleotide polymorphisms (SNPs) and DNA methylations) in the specific genes that are associated with stress response in humans.

Gene-environment interaction in psychopathologies: Stress and SNPs

The adverse health outcome of stressful life events can be explained by the diathesis-stress model (Meehl, 1962). Aligned with the model, biological predispositions together with stressful life experiences may result in psychopathologies. Studies have reported significant relationships between specific SNPs (i.e., different alleles caused by mutations in a single nucleotide that occur when copying the DNA) in the stress-related genes and psychopathologies (Ising et al., 2008; Plomin et al., 2013).

Brain-derived neurotrophic factor (BDNF) gene is associated with stress response, brain plasticity, and neural connection in high-order cognitive functions. Studies showed that SNPs in BDNF interacted with stressful life experiences and predicted psychiatric conditions such as depression, anxiety, and post-traumatic stress disorder (PTSD) (Gatt et al., 2009; Jin et al., 2019). Studies also found that SNPs in the hypothalamus-pituitary-adrenal (HPA) axis regulating genes (corticotropin releasing hormone receptor 1 (CRHR1), FK506 binding protein prolyl isomerase 5 (FKBP5) and corticotropin releasing hormone binding protein (CRHBP)) were related to several psychopathologies (e.g., depression and PTSD, and suicide attempts)

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✉ **Esra Zıvralı Yarar** · esra.yarar@asbu.edu.tr | [1]Ph.D., Department of Psychology, Social Sciences University of Ankara, Ankara, Turkey.
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through interacting with early adverse life experiences (Binder et al., 2008; Bradley et al., 2008; Polanczyk et al., 2009; Roy et al., 2012; Wang et al., 2018). Findings indicate that SNPs in stress-regulating genes play an important role in the relationship between stressful life experiences and psychopathologies. Significant interactions especially between early stressful experiences and psychopathologies may be explained by developmental problems in stress-regulating mechanisms in critical periods (Gee & Casey, 2015; Heim & Binder, 2012).

Psychopathology and epigenetics

Twin method has been used to unravel genetic and environmental factors of several phenotypic differences, including psychopathologies. The phenotypic discordance between monozygotic (MZ) twin pairs may be due to some genetic and epigenetic reasons (Kato et al., 2005; Meaney, 2010). The dynamic and operational genomic approach has been replaced with the stable compositional genomic approach (i.e., DNA sequence) to investigate the phenotypic discordance between MZ twin pairs. Epigenetic research shows that taking the function as well as the composition of the genes into consideration is essential to understand gene-environment interaction for individual differences (Meaney, 2010). DNA methylation is the most studied epigenetic mechanism amongst the other known epigenetic variations for psychological problems (Meaney, 2010; Mill et al., 2006). Depending on where the DNA methylation occurs on a gene, the gene can be silenced or expressed affecting the functioning (Docherty & Mill, 2008; Stricker et al., 2017).

Gene-environment interaction in psychopathologies: Stress and DNA methylation

DNA methylation profiles of stress-related genes have been studied to understand the relationship between stressful life experiences and psychopathologies (Januar et al., 2015; Klengel et al., 2014). Specifically, the well-known relationship between early adverse life events and psychopathologies later in life may be explained by the role of DNA methylation in the genes regulating stress response (Barker et al., 2018). Since the earliest stage of development, stressful life events may be interacting with the stress-related biological mechanisms altering the expression of the responsible genes and leading to psychopathologies in adulthood (Babenko et al., 2015; Bakusic et al., 2017; Glover et al., 2018). DNA methylation differences in specific stress-related genes (e.g., nuclear receptor subfamily 3 group c member 1 (NR3C1) gene) may explain the relationship between adverse events before birth and psychopathologies such as anxiety, depression, and PTSD later in life (Hompes et al., 2013; Oberlander et al., 2008; Perroud et al., 2014; Radtke et al., 2011). Stressful life experiences after birth (both in childhood and adulthood) have also been reported to be linked to psychopathologies, such as personality disorders, PTSD, and suicide behavior through DNA methylation mechanisms in NR3C1 and serotonin transporter gene SLC6A4 (Beach et al., 2011, 2013; Labonte et al., 2012; McGowan et al., 2009; Yehuda et al., 2015). The findings have highlighted that DNA methylation differences on specific genes regulating stress response may be responsible for vulnerability/resilience to several psychopathologies (Duman & Canli, 2015; Maud et al., 2018; Palma-Gudiel et al., 2015).

Stress-related genetic and epigenetic mechanisms in the treatment of psychopathologies

Understanding SNPs and DNA methylation profiles of stress-related genes is also helpful for understanding the effectiveness of treatments for psychopathologies. SNPs in CRHR1 and DNA methylation differences in SLC6A4, BDNF, FKBP5 and NR3C1 have been reported to be related to treatment effects of several psychopathologies, such as depression, bipolar disorder, PTSD, anxiety, and borderline personality disorder (Booij et al., 2015; Carlberg et al., 2014; D'Addario et al., 2012, 2013; Liu et al., 2007; Perroud et al., 2013; Roberts et al., 2014, 2015; Yehuda et al., 2013). Findings indicated that the diversity recorded on the effectiveness of different medication and psychotherapy techniques might be related to individual differences in SNPs and DNA methylations in stress-related genes.

Limitations and suggestions

Despite being helpful in understanding the dynamic relationship between nature and nurture, findings of studies on the complicated relationship amongst stressful life experiences, stress-related genes and psychopathologies must be considered with their limitations. Polygenic and overlapping mechanisms of psychopathologies, data mostly depending on buccal/blood cells and causality problems are some of the most cited limitations which are likely to negatively affect the generalizability of results (Bakulski et al., 2016; Hannon et al., 2015; Kumsta, 2019; Smoller et al., 2019).

Conclusion

The nature-nurture debate seems to be evolving into understanding the relationship and interaction between

the two and learning more about relevant mechanisms. Genetic and epigenetic effects interacting with negative life experiences suggest a possible explanation for etiology and treatment of psychopathologies. Especially SNPs and DNA methylation differences in stress-regulating genes may help with understanding and treating psychopathologies effectively.

Conflict of Interest The author(s) declare that there is no conflict of interest.

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