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Molecular genetics and attention in ADHD

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Abstract

A research program at UC Irvine has investigated the molecular genetic basis of ADHD by focusing on one candidate gene (DRD4) and the highly variable 48 bp VNTR polymorphism in exon 3. Initial studies revealed that the 7R variant is over-represented in ADHD samples, and a subsequent study suggested that the 7R allele is associated with clear excesses in behavior but not with some cognitive deficits thought to be core feature of the disorder. The next phase of this research program showed that (1) the common 7R allele was the product of positive selection, (2) other variation in and around the *DRD4* gene is in tight linkage disequilibrium with the 7R allele but not the 4R allele, and (3) more rare 7R variants in the ADHD clinical sample than expected. Based on this program of research, we suggest that the 7R VNTR variant is responsible for the observed association of the DRD4 gene with ADHD, and that a challenge for the future is understanding what other genetic and/or environmental factors influence this association and affect clinical outcome of the disorder.

Keywords: ADHD; DRD4; Nucleotide sequence; Resequencing; Positive selection; Common disorder/common variant (CDCV) hypothesis

1. Background on genetics

Attention Deficit Hyperactivity Disorder (ADHD) has multiple causes, including some that are environmental and some that are genetic [39,41]. In the past, most evidence of the genetic basis of ADHD was obtained from the evaluation of ADHD symptoms in family members (ADHD runs in families and in twins (if one twin has ADHD it is more likely for identical than fraternal twins to exhibit the disorder resulting in an estimated heritability of ~0.8). These statistical genetic findings stimulated molecular genetic studies of ADHD, using genome scan methods (to identify chromosomal locations likely to be harboring genes associated with ADHD) using standard methods [33–38] with some dificulty as expected [40] and candidate gene approaches (to evaluate the association of specific genes with ADHD).

The first published molecular genetic studies of ADHD were centered on the neurotransmitter dopamine (DA), including (1) the *Dopamine Deficit Theory of ADHD* [1,2] (2) the *Neuroanatomical Network Theory of Attention* [3] and (3) the *Site of Action of Stimulant Medications* [1,4]. Based on these theories, the initial candidate gene studies of ADHD focused on two DA genes whose locations were known (see Fig. 1); the DA transporter gene (*SLC683* or *DAT*) on chromosome 5 (5p15.3) and the DA receptor type 4 (*DRD4*) gene on chromosome 11 (11p15.5). Each of these genes has well-documented variation across individuals (polymorphism) due to segments of DNA that are repeated a variable number of times, called a 'variable number of tandem repeats' (VNTR).

The DAT gene has polymorphic 40 base-pair (bp) VNTR in a non-coding region of the gene. In European ancestry populations, the primary allelic variations are defined by 10 repeats of the VNTR (characteristic of about 74% of alleles), 9 repeats of the VNTR (characteristic of about 25% of alleles), or 3 repeats of the VNTR (characteristic of about 1% of alleles). Because a primary mechanism of action of methylphenidate, a common medication in ADHD treatment, is the inhibition of reuptake of DA [4,5], the possibility of DAT overactivity (resulting in a 'dopamine deficit') has been hypothesized as a factor in ADHD [6,7].

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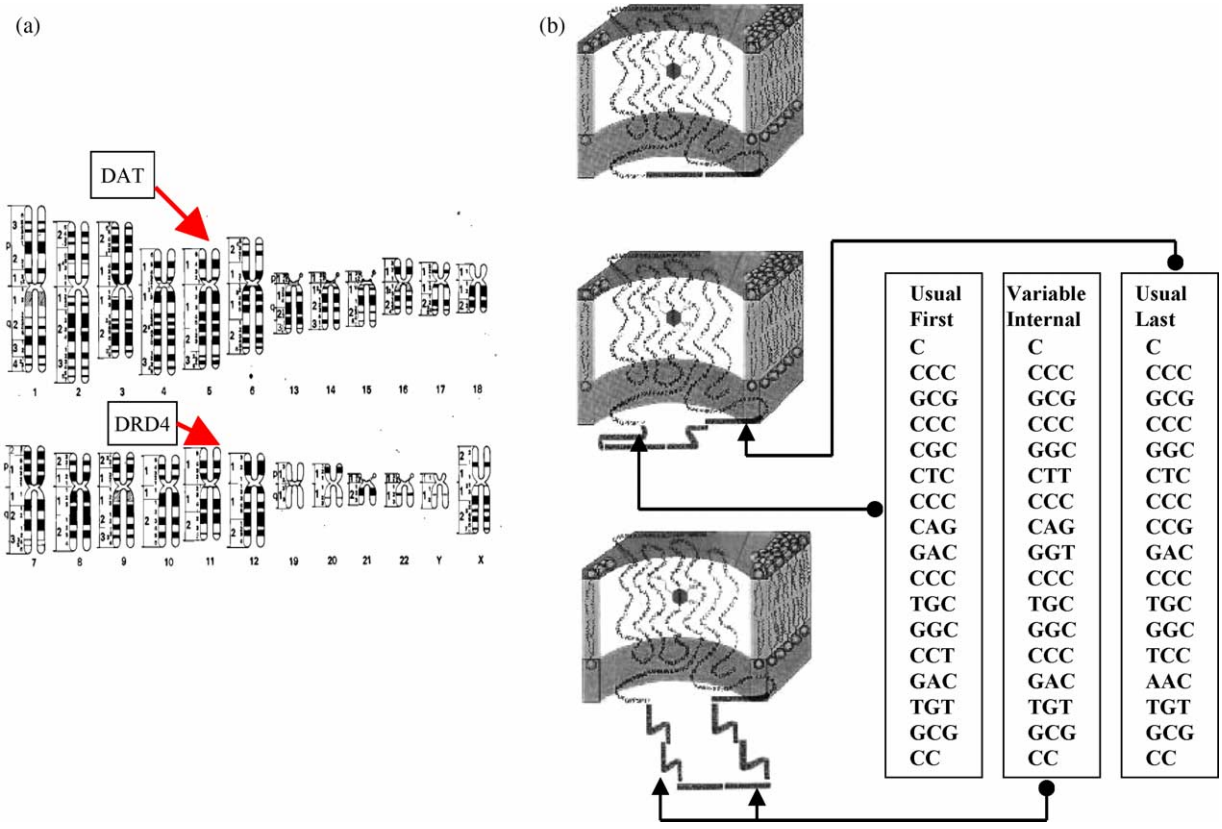

Fig. 1. (a) Chromosome locations of the *DAT* (5p) and *DRD4* (11p) genes and (b) three primary alleles of the DRD4 gene based on the 2, 4, and 7 repeats of the 48 bp VNTR in exon 3.

In a family-based association study, [6] reported an increased frequency of transmission of the most prevalent allele (10 repeat) in an ADHD sample. Subsequently, others have replicated this finding [8,9], but some have not [7,10,11]. Non-replication with small samples is expected when the frequency of the risk allele increased less than 50% in the clinical sample relative to the control sample (i.e. with a relative risk <1.5), but a meta-analysis [35] has provided clear support for the overall statistical significance of the association of DAT with ADHD. However, this will not be discussed here, since at UCI we have focused on the *DRD4* gene and its association with ADHD.

The *DRD4* receptor is one of the five DA receptors that have some common characteristics (i.e. seven transmembrane units) and some differences (i.e. size of the 3rd transmembrane loop). The *DRD4* gene has a polymorphism (a 48 base-pair VNTR, with 2–11 repeats) that was investigated in studies of schizophrenia see [12], personality dimensions see [13], and basic synaptic function see [14,15] before the first investigation of ADHD [16]. This background provided detailed information on *DRD4* in the human population. For example, [12] described how the allele frequencies of *DRD4* vary across ethnic groups and estimated the frequencies in a sample of 150 unrelated Caucasians: 4R ∼67%, 7R ∼12%, 2R ∼10%, others ∼11%. This variation in a coding region (exon 3; see Fig. 1d) of the *DRD4* gene produces differences across individuals in the size of an important region of the dopamine receptor, the 3rd intracellular loop that couples to G-proteins and mediates post-synaptic effects.

2. Initial studies at UCI on the molecular genetics of ADHD

The molecular genetic studies of ADHD at UC Irvine were initiated in 1994 in collaboration with a group from the Clarke Institute of Psychiatry in Toronto (led by James Kennedy and Cathy Barr). [17] described the rationale for choosing the *DRD4* as a candidate gene, which is dense in the frontal cortex and may have some alleles that are subsensitive to dopamine resulting in a deficit in the output of dopamine receptive neurons and [18]. The first study ([16]; see Fig. 2a) used a simple population-based design, in which DNA from a group of individuals with ADHD was compared to an 'ethnically matched' control group. The second study used a family-based design [19]; see Fig. 2b, in which DNA from probands with ADHD was compared to a 'perfectly matched' theoretical control defined by untransmitted parental alleles.

In these studies, the 7R allele was found to be overrepresented in the ADHD group. In the population-based

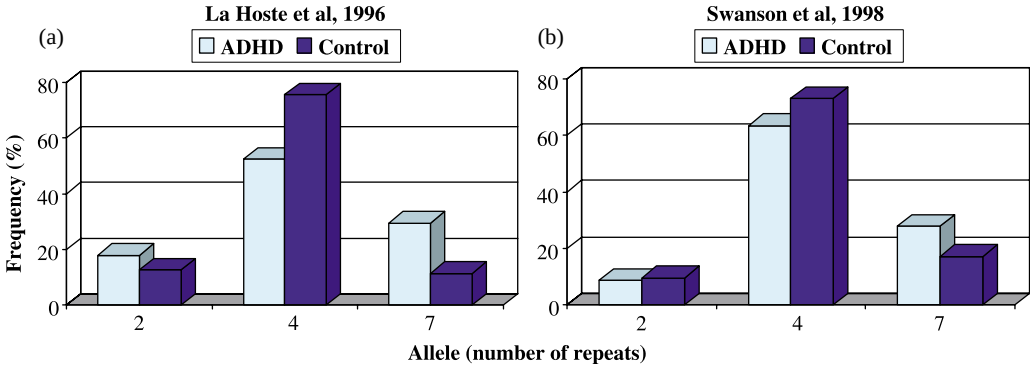

Fig. 2. (a) Children with ADHD have an increased prevalence of the 7R allele compared to a non-ADHD control subjects and (b) children with ADHD have an increased prevalence of the 7R allele compared to theoretical control group defined by the non-transmitted parental alleles. Adapted from [16,42].

association study, almost 30% of the alleles in the ADHD sample were 7R variants, compared to about 12% in a control sample (see Fig. 2a). In the family-based association study, about 28% of the alleles transmitted to ADHD probands were 7R variants, compared to 18% of the allele not transmitted (see Fig. 2b). In these studies, the genotype was based on individuals with at least one 7R allele (labeled the 7+ genotype) and those did not (labeled the 7− genotype). About 50% of the ADHD cases had the 7+ genotype and about 50% the 7− genotype, while in the control group, about 20% had the 7+ genotype and 80% had the 7− genotype.

These two studies provided an initial piece of the molecular genetic puzzle about ADHD: the 7R allele was 'associated' with the diagnosis of ADHD. This left open the possibility that in some cases some of the symptoms of ADHD may be caused (at least in part) by the *DRD4* gene.

As discussed above, the small sample sizes commonly used in association studies often result in non-replication see [20]. Among other factors, the high 'false positive' rate occurs partly because there are so many genes (at least 30,000) that someone's 'educated guess' may result in a chance finding. In contrast, the association of ADHD with an increase in the 7R variant of the *DRD4* gene has been confirmed by so many research teams around the world see [7,21] that it has stood as one of the most reliable genetic findings yet reported for the association of a gene with specific behavior see [22].

3. The DRD4 genotypes and specific deficits of attention

The next step in the UCI research program was to find out whether this difference in DNA was related to specific deficits of attention. DNA was obtained from a group of children entered in the Multimodality Treatment study of ADHD (MTA), and neuropsychological tests were administered to measure the attention deficits associated with ADHD. The literature shows that the typical pattern of response on three widely used tests (the Stroop color-word test, the Logan stop-signal task, and the Posner spatial-cueing task) is characterized by slower and more variable reaction times to words and symbols.

The hypothesis was that the subgroup of ADHD children with the 7+ genotype (about half the group) would show an attention deficit on these tests and that the other subgroup would not. The opposite was observed [23]. Even though both the 7+ and 7− subgroups had behavioral symptoms of ADHD (i.e. an entry criterion for the MTA was high symptom ratings, and the two subgroups did not differ on the SNAP rating scale), only the subgroup without a 7R variant (the group with the 7− genotype) showed an attention deficit reflected by slower and more variable than normal reaction times (see Fig. 3) on the Stroop color-word task, the Posner cued-detection task, and the Logan stop-signal task. This provided a second piece in the molecular genetic puzzle about ADHD: the subtype associated with the *DRD4* gene may have a different manifestation (phenotype) of ADHD than the subtype associated with other causes of ADHD.

Recently, two independent groups partially replicated and extended this finding. [24] demonstrated that a 7+ subgroup of ADHD children had even faster than normal reaction time on a task similar to one from the [7] protocol (the Logan stop-signal task).

4. Refining the DRD4 genotype

After this study, the ADHD molecular genetic research program was redirected by investigating DNA variation in a new way to gain a better understanding of the variation in exon 3 of the *DRD4* gene. Instead of just measuring the length of the *DRD4* VNTR, the new and more efficient technology for DNA sequencing (which was a byproduct of the Human Genome Project) was used. This offered an opportunity to determine the *sequence* of the basic building blocks of DNA ('nucleotides') and to investigate the ancient origins of the different variants of DNA in the *DRD4* gene now present in the human population.

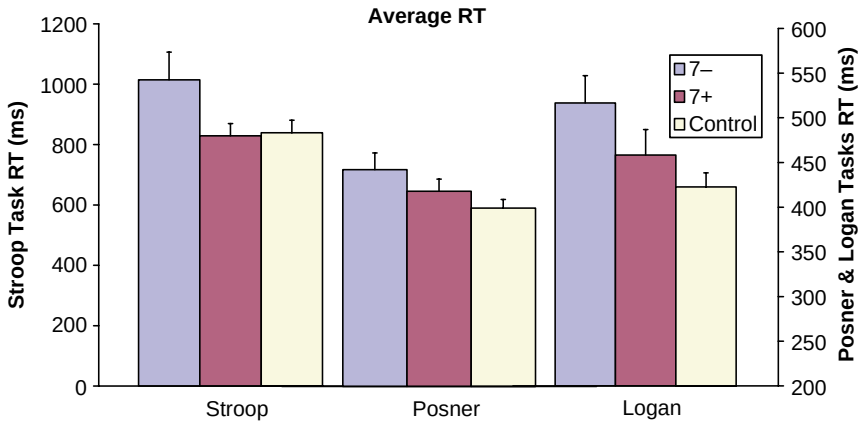

Fig. 3. ADHD children with the 7+ genotype have extreme behavior but near normal reaction time performance on critical neuropsychological tests. Adapted from [7], PNAS, vol. 97:4754–4759.

Initial studies uncovered a high frequency of *DRD4* sequence variants in ADHD probands. Many genes exhibit sequence variation between different human populations, likely the result of random genetic drift. Hence, it was important to sample a worldwide population to rule out that unintentional stratification was causing our ADHD results despite the predominantly European ancestry of our probands. [25] reported the results of a survey of DNA sequences from a worldwide sample of 600 alleles. The exon 3 VNTR was sequenced for each allele. The patterns found see Fig. 4 revealed an unusual pattern of nucleotide variation. First, the 48 bp repeat sequence of the VNTR was 'imperfect' and had even more variability than had previously been reported by [26]. We labeled the variety of 48 bp repeat sequence 'motifs' with numbers. The proposed ancestral allele (4R) almost always consisted of the 1–2–3–4 combination of motifs (a $48 \times 4 = 192$ nucleotide sequence). The similarity in motifs of other alleles suggested that asymmetric recombination had produced these variants, i.e. two 4R alleles could recombine to form a 2R (the 1–4 combination of motifs) and a 6R (the 1–2–3–2–3–4 combination of motifs). However, the 7R allele was very dissimilar from the ancestral 4R sequence. We observed that multiple recombinations and mutations from the ancestral 4R sequence would be required to generate the observed motif combination (i.e. 1–2–6–5–2–5–4) of the typical 7R allele (a $48 \times 7 = 336$ nucleotide sequence).

Based on these sequencing results, a hypothesis was proposed that the original (ancestral) exon 3 variant of the *DRD4* gene was the 4R allele, but that over time, the mixing of DNA by the process of recombination produced most of the other variants (i.e. the 2R, 3R, 5R, and 6R alleles) but not the 7R variant. The unusual nucleotide sequence of the 7R allele would require the co-occurrence of several other processes that infrequently produce changes in DNA. Such rare changes in a VNTR usually do not spread to become a common variant. Using standard statistical methods for analysis of DNA sequences, [25] estimated that the 7R allele arose not long ago by evolutionary standards (about 50,000 years ago). This unusual 7R variant increased from a low frequency to become a 'common' allele (10–20% in the worldwide sample).

Based on the unusual DNA sequence organization of the 7T allele, yet a high population frequency, [25] proposed that the increase in frequency was due to positive selection; [27]. Further work by [28], discussed below, lent additional support to this hypothesis. This provides a third piece in the molecular genetic puzzle about ADHD, i.e. the 7RDNA variant associated with ADHD emerged in the human population recently (about 50,000 years ago) and, instead of being eliminated due to detrimental effects, it increased in frequency, probably because it conveys some benefits to its carriers (at least under some circumstances).

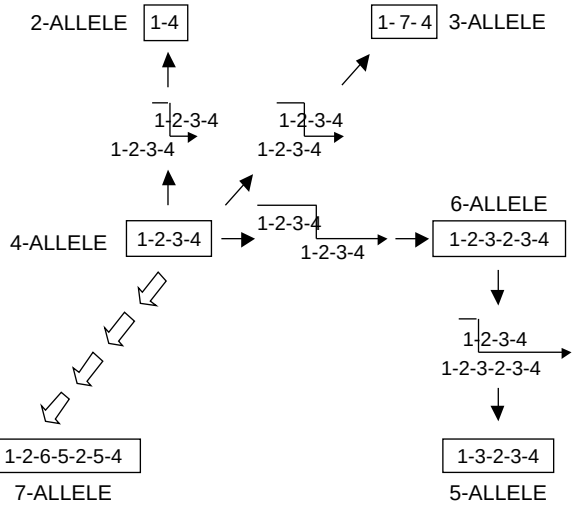

Fig. 4. The theoretical origins of alleles (except for 7R) by recombination. Adapted from [25].

[25,29] reinterpreted why the 7R allele may be associated with a personality characteristic see: [13,30,31] the characteristic of 'novelty seeking' may have contributed to the spread of an original small human population by migration out of Africa into Europe and Asia, and across the Bering Strait and into the Americas (first into North America and then into South America). In fact, the allele frequency of *DRD4* 7R in different geographic locations appears to be correlated with the distance the various groups are inferred to have migrated see.[29]

5. Sequence analysis of the DRD4 gene in DNA from an ADHD sample

Based on this evolutionary biology approach, an investigation was initiated to understand why a 'beneficial' allele (7R) would now be associated with a 'disorder' (ADHD). [32] obtained DNA from 132 ADHD individuals and obtained the nucleotide sequences for 250 alleles from this clinical sample (see Fig. 5). Analysis of sequences of the exon 3 VNTR showed that over 10% of the ADHD cases had a 7R variant that had not been seen in our large worldwide sample (and thus we called these 'rare' variants). This provided a fourth piece in the molecular genetic puzzle about ADHD: in addition to the common 7R variant, many rare 7R variants are present in the DNA of children with ADHD.

[28] resequenced the entire *DRD4* locus from 103 individuals homozygous for 2R, 4R, or 7R variants of the VNTR, a method developed to directly estimate haplotype diversity. ADHD individuals were included in this sample. DNA from individuals of African, European, Asian, North and South American, and Pacific Island ancestry were used. A large number ($n=71$) of single nucleotide polymorphisms (SNPs) was discovered in and surrounding the *DRD4* gene. As shown in Fig. 6 (a plot of 71 SNPs in the columns by 103 individuals in the rows). The 4R/4R homozygotes exhibited little linkage disequilibrium (LD) over the region examined. In contrast, there was strong evidence of LD in the 7R/7R homozygotes. In addition, the pattern of LD in the 2R/2R homozygotes suggested that the 2R allele was derived from a recombination of 7R allele with 4R allele, producing a pattern of high LD, identical to the 7R allele, downstream from the VNTR.

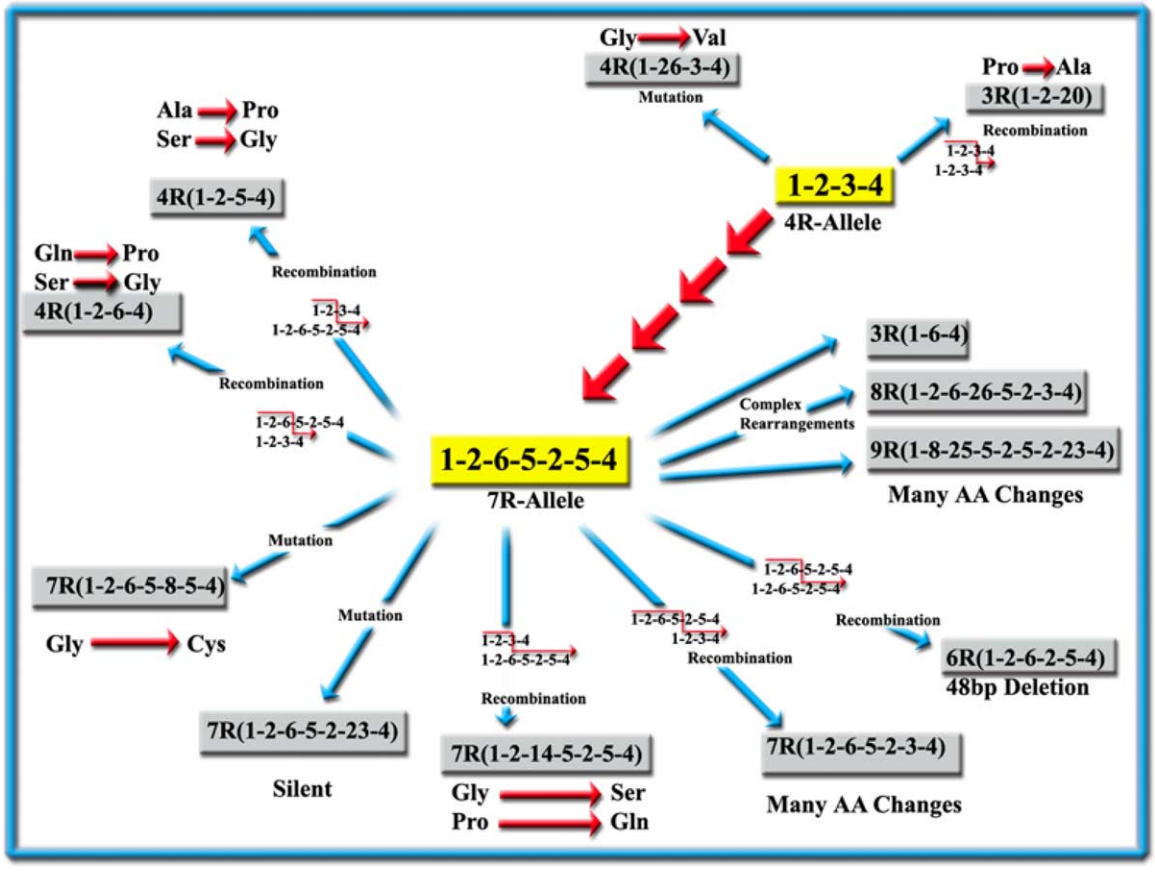

Fig. 5. The modal 7R nucleotide sequence is defined by 'motifs' 1–2–6–5–2–5–4, and this 7R allele occurs more frequently in ADHD groups than in control groups. In addition, the unusual nucleotide sequences occur more frequently in ADHD groups, and most of the unusual sequences are derived from recombinations of 7R alleles. Adapted from [32], Molecular Psychiatry, vol. 8:536–545.

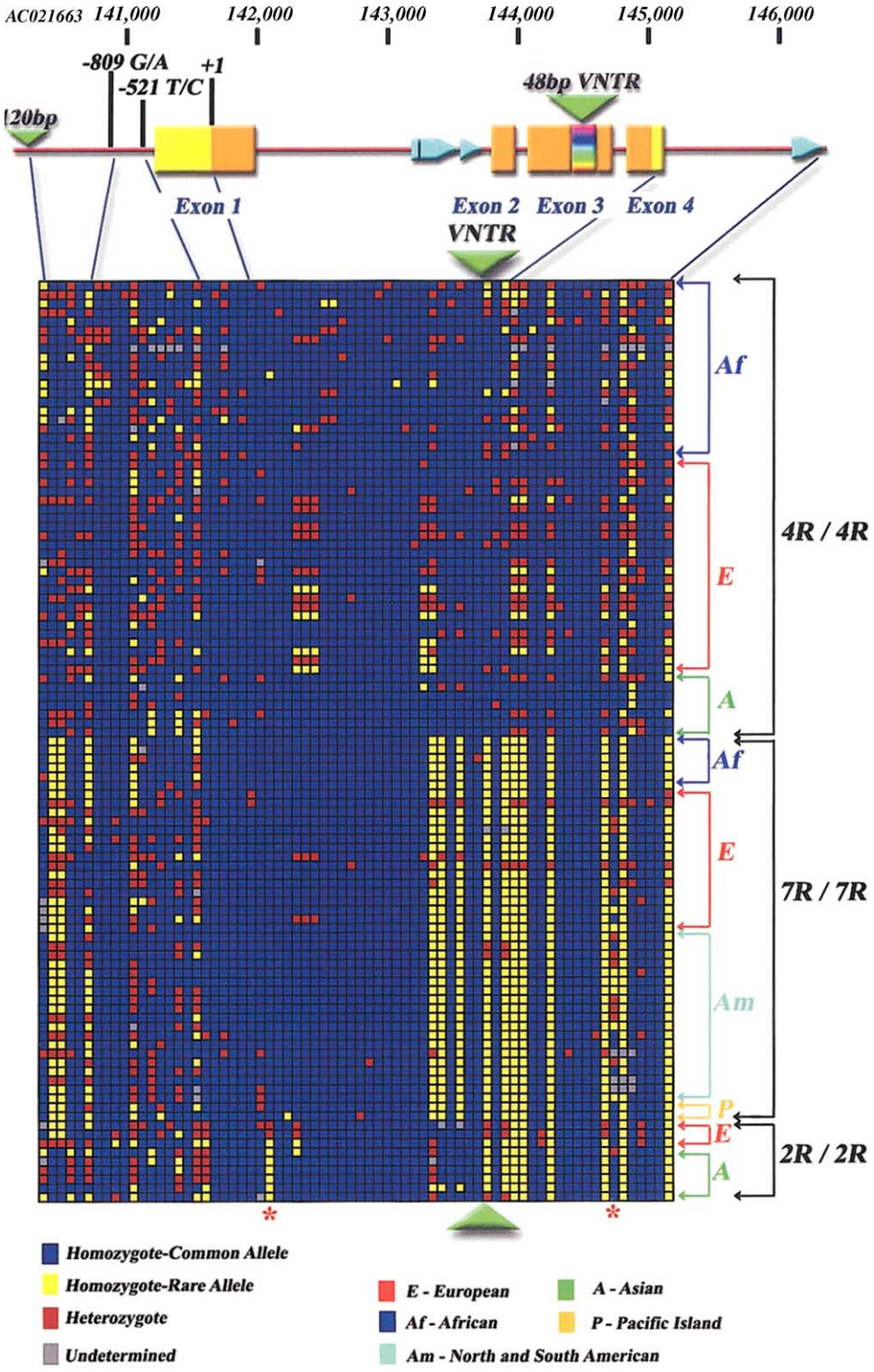

Fig. 6. Linkage disequilibrium in a set of 71 SNPs in the DRD4 gene. Adapted from [28].

All 7R/7R individuals (including those with ADHD) exhibit exactly the same alleles at most polymorphic sites. By intra-allelic comparison at 18 high-heterozygosity sites spanning the locus, we estimate that the 7R allele arose prior to the upper Paleolithic era (40,000–-50,000 years ago). Further, the pattern of recombination at these polymorphic sites is the pattern expected for selection acting at the 7R VNTR itself, rather than at an adjacent site. We propose a model for selection at the *DRD4* locus consistent with these observed LD patterns and with the known biochemical and physiological differences between receptor variants [28].

6. Summary of the UCI research program: where are we now?

The research program at UC Irvine has provided four pieces of the molecular genetic puzzle about ADHD. (1) A variety of DA theories of ADHD led to the use of the *DRD4* gene in the initial molecular genetic studies of this disorder (see Fig. 1); the 7R variant is over-represented in ADHD samples (see Fig. 2); (2) the 7R allele is associated with clear excesses in behavior but not with some cognitive deficits in attention thought to be the defining features of ADHD (see Fig. 3); (3) the common 7R allele was the product of positive selection and thus was beneficial, not detrimental, in human evolutionary history (see Fig. 4); other variation in and around the *DRD4* gene is in tight linkage disequilibrium with the 7R allele but not the 4R allele (see Fig. 5); (4) the DNA in a typical clinical group of ADHD individuals has many more rare 7R variants than would be expected from a worldwide survey of DNA (see Fig. 6). In conclusion, collectively these results suggest that the 7R VNTR variant, not another tightly linked polymorphism, is responsible for the observed association with ADHD. What is the next step? A study of the molecular genetics of ADHD children in the full Multimodal Treatment study of ADHD (MTA) sample of 579 children with ADHD Combined Type was initiated in 2003, with support provided by the National Institute of Neurologic Disorders and Stroke (NINDS). Twenty-five to 50% of attributable genetic risk appears to be associated with DRD4 7R. The challenge for the future is to understand what other genetic and/or environmental factors influence this association and its relevance for the clinical outcome of the disorder.

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