ANKRD6 Genetic Variants Influence Habitual Physical Activity Levels

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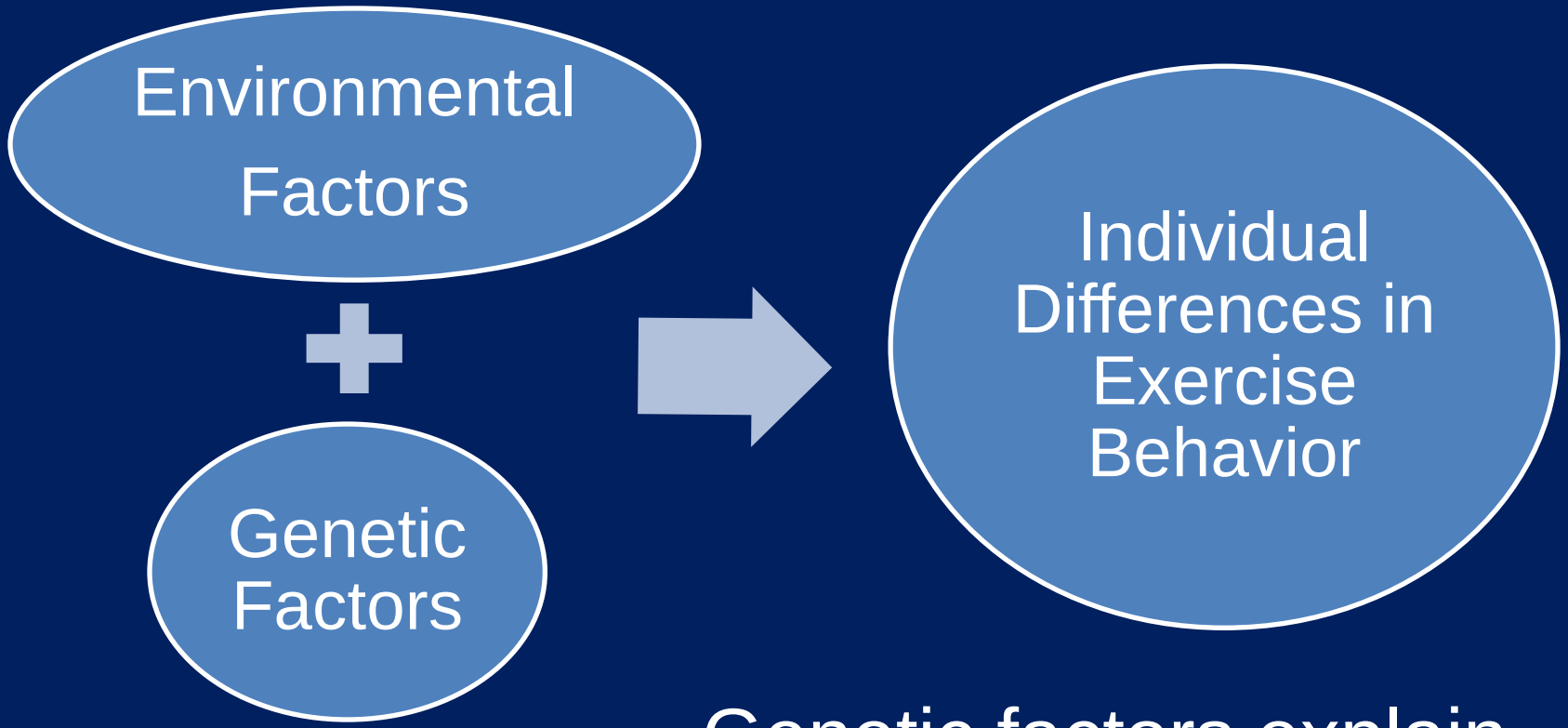
Genes and Physical Activity (PA)

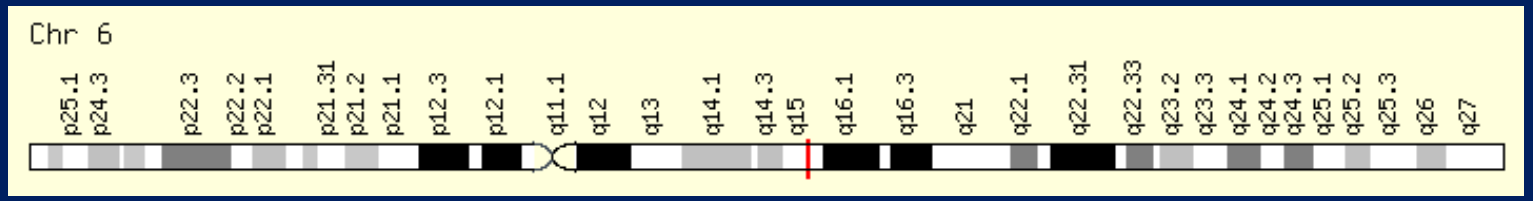


Genetic factors explain 32-85% of variation in adult PA levels[1,2,3]

1. De Moor et al., Eur J Epidemiol (2007) 22, 27-32
2. Carlsson et al., MSSE (2006) 38, 1396-1401
3. Simonen et al., MSSE (2004) 36(9), 1559-1566

ANKRD6 (Diversin)

- Location: chromosome 6q14.2-q16.1
- Transcribed as a 5.8-kb mRNA composed of 15 exons that encodes a 727 AA protein with 6 ankyrin repeats

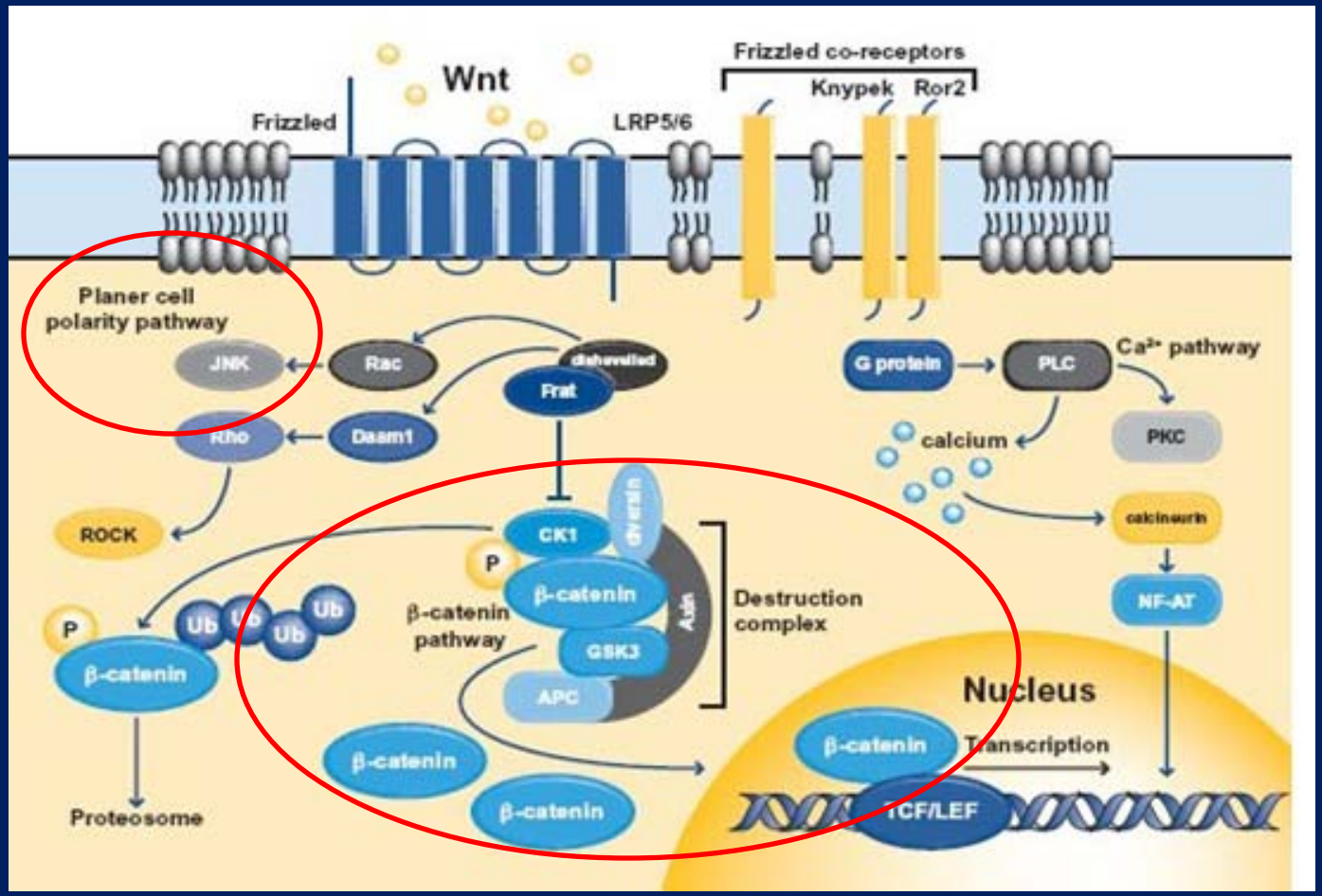


ANKRD6 (Diversin)

- Associates with brain development, axis formation, and heart formation in mammals, and is highly expressed in the brain, spinal cord, and heart of humans.

Wnt Signalling Pathway

PCP pathway



beta-catenin pathway

Schwarz-Romond et al., Genes & Dev. 2002 16: 2073-2084.

Purpose

- We examined if 9 ANKRD6 SNPs associate with habitual physical activity levels among healthy, young adults.
  - 550 A>T, 545 T>A, 485 M>L, 233 T>M, 128 V>I, 636 P>L, 122 Q>E, 97805 G>A, 710 L>X
- We also examined if ANKRD6 haplotypes associate with habitual physical activity.

Subjects

- Functional single nucleotide polymorphisms Associated with human Muscle Size and Strength (FAMuSS)[1]
  - Designed to identify genes associated with muscle performance
- Total ANKRD6 sample included 536 healthy Caucasian men and women, 18-39 yr

Paffenbarger PA Questionnaire (PPAQ)[1]

- Each subject completed the PPAQ
- PA phenotypes included:
  - Hr/wk participating in:
    - Vigorous intensity PA
    - Moderate intensity PA
    - Light intensity PA
    - Sitting
  - Kcal/wk participating in:
    - Vigorous intensity PA
    - Moderate intensity PA
    - Sports

1. Paffenbarger et al., American Journal of Epidemiology (1978) 108, 161-175.

Genotyping

- DNA was extracted from blood samples of all subjects
- Polymerase chain reaction (PCR) was used to generate copies of DNA
  - Genotyping was performed using a novel TaqMan allelic discrimination assay
  - Results were confirmed using restriction enzyme analysis

Statistical Analysis

- Subject Characteristics
  - Descriptive statistics
- CHI-squared for Hardy-Weinberg Equilibrium (HWE)[1]
- SPSS 14.0
- Multivariate ANCOVA
  - Independent Variables
    - Genotype
    - Gender
  - Covariates
    - Age
    - BMI
  - Significance
    - $p<0.05$

1. Santiago Rodriguez, Tom R. Gaunt and Ian N. M. Day. Hardy-Weinberg Equilibrium Testing of Biological Ascertainment for Mendelian Randomization Studies. American Journal of Epidemiology. 2009.

Subject Characteristics
(Mean ± SEM)

	Total Sample (n = 536)	**Men (n = 242)**	**Women (n = 294)**
Age (yr)	23.4 ± 0.2	23.7 ± 0.3	23.2 ± 0.3
BMI (kg/m2)	24.6 ± 0.2	25.3 ± 0.3	23.9 ± 0.3*

* Men vs. Women, $p<0.05$

ANKRD6 128 I>L/636 P>L Haplotypes

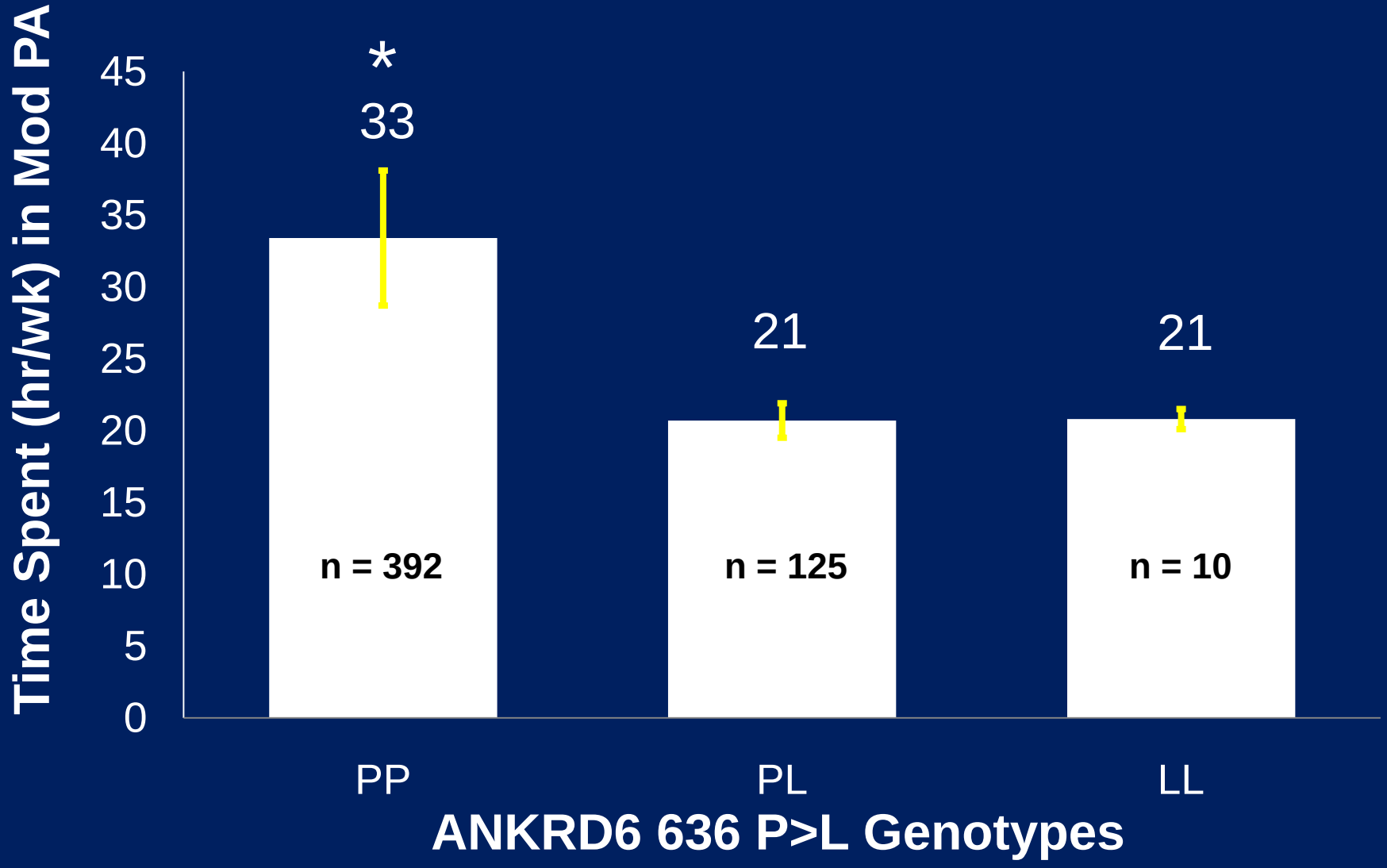
Haplotype	n
II/PP	2
IL/PL	**111**
LL/LL	0
II/PL	4
II/LL	8
IL/PP	**25**
IL/LL	2
LL/PP	**364**
LL/PL	**10**

ANKRD6 128I>L/636P>L in LD (r2 = 0.55)

Common Haplotypes (4) = 97% of the total ANKRD6 128I>L/636P>L sample

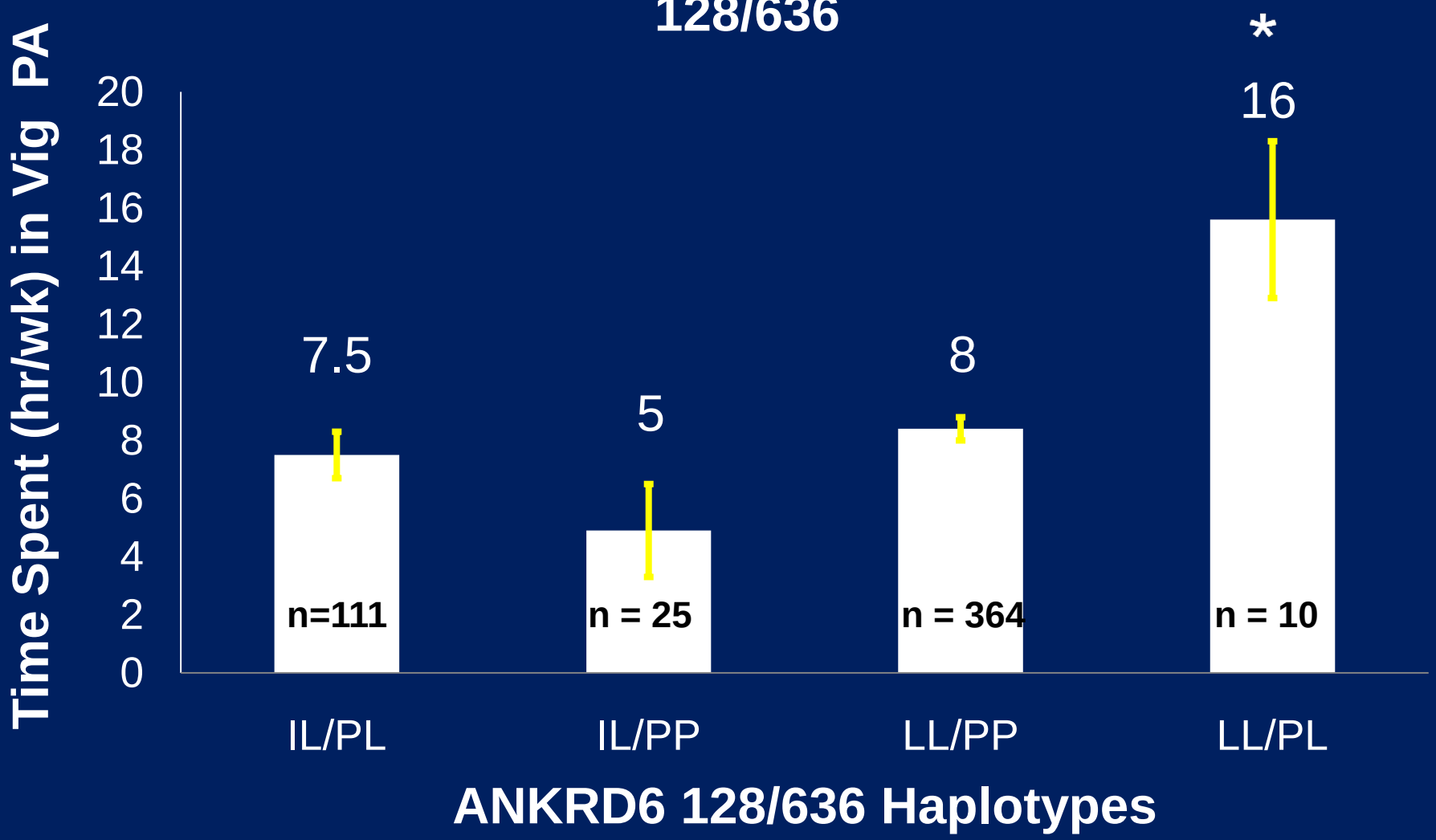
Results

Time Spent (hr/wk) in Moderate Intensity PA among Total Sample by ANKRD6 636 P>L



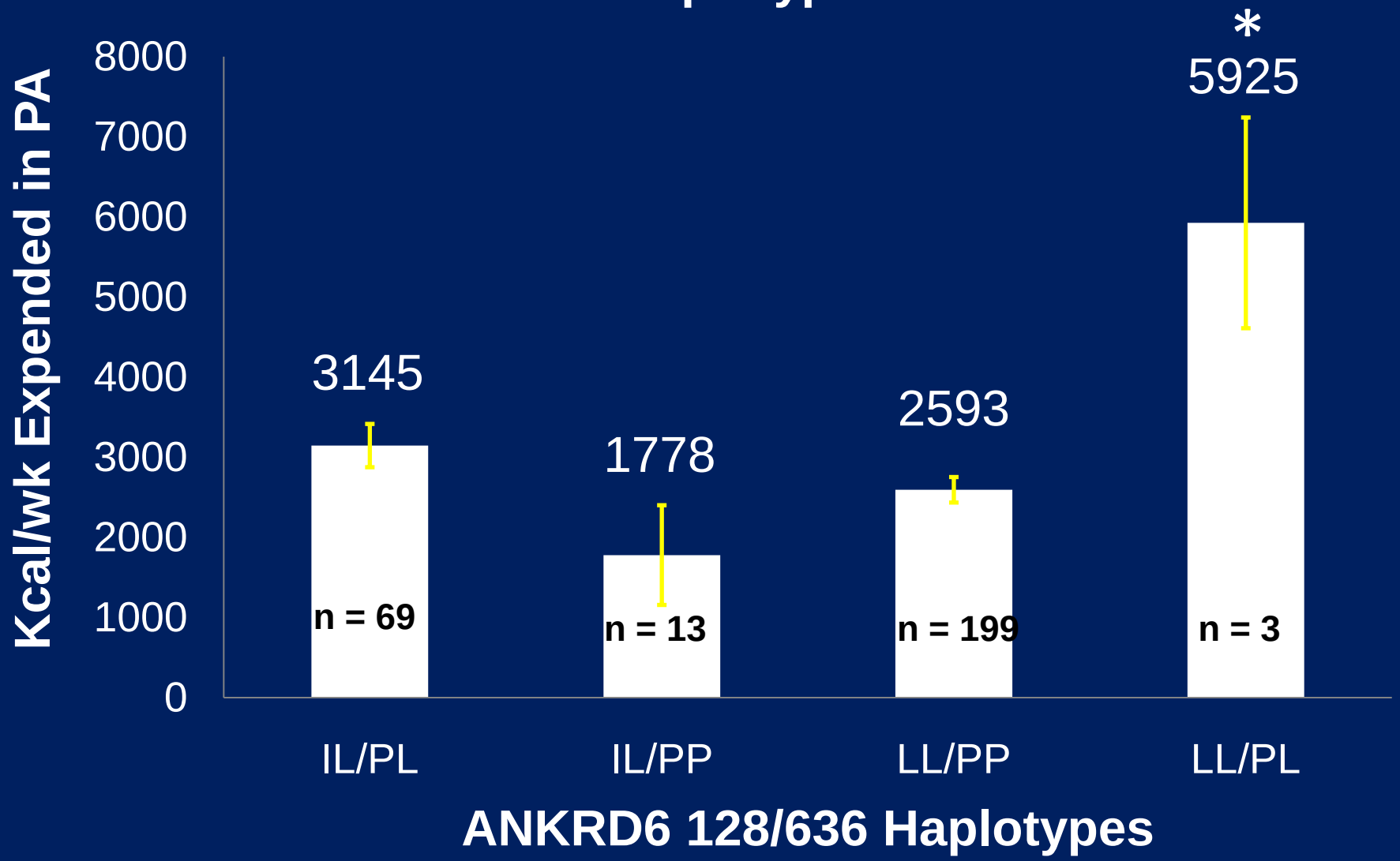
* = PP vs. PL , PP vs. LL, $p<0.05$

Time Spent (hr/wk) in Vigorous Intensity PA among Total Sample by ANKRD6 Haplotype 128/636



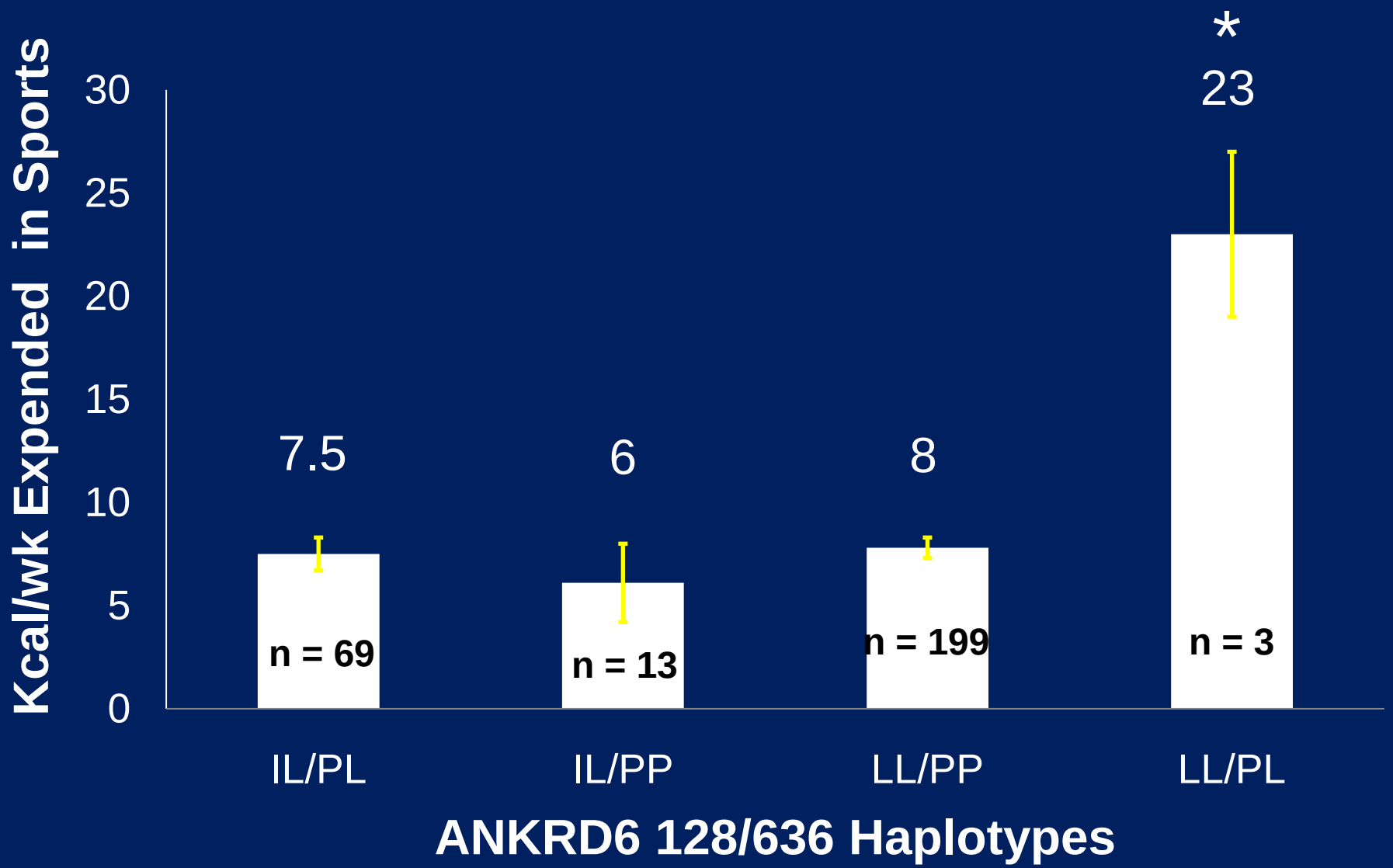
* = LL/PL vs. IL/PL; LL/PL vs. IL/PP , $p<0.05$

Kcal/wk Expended in PA among Women by ANKRD6 Haplotype 128/636



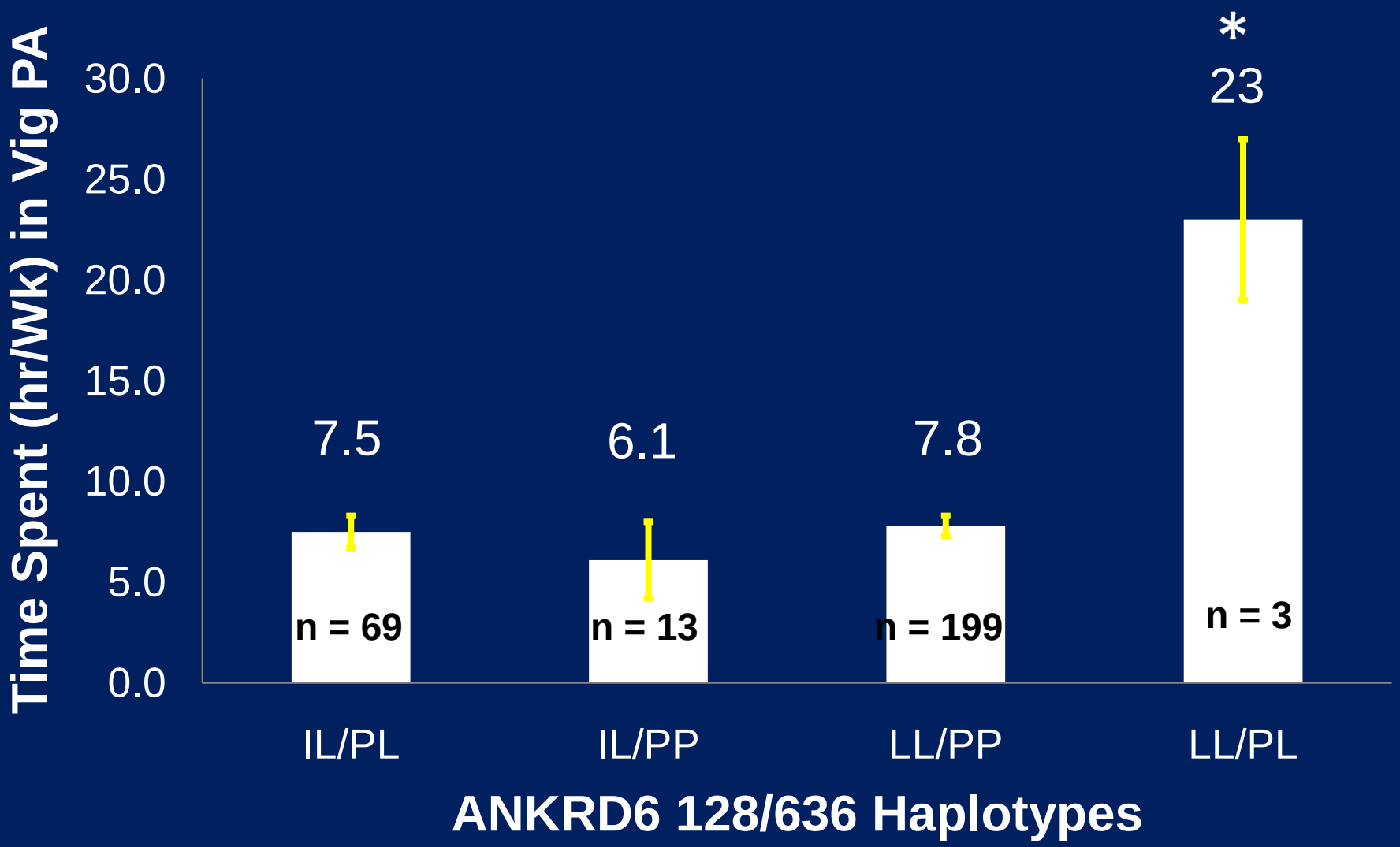
* = LL/PL vs. IL/PP, p<0.05

Kcal/wk Expended in Sports among Women by ANKRD6 Haplotype 128/636



* = LL/PL vs. IL/PP p<0.05

Time Spent (hr/wk) in Vigorous Intensity PA among Women by ANKRD6 Haplotype 128/636



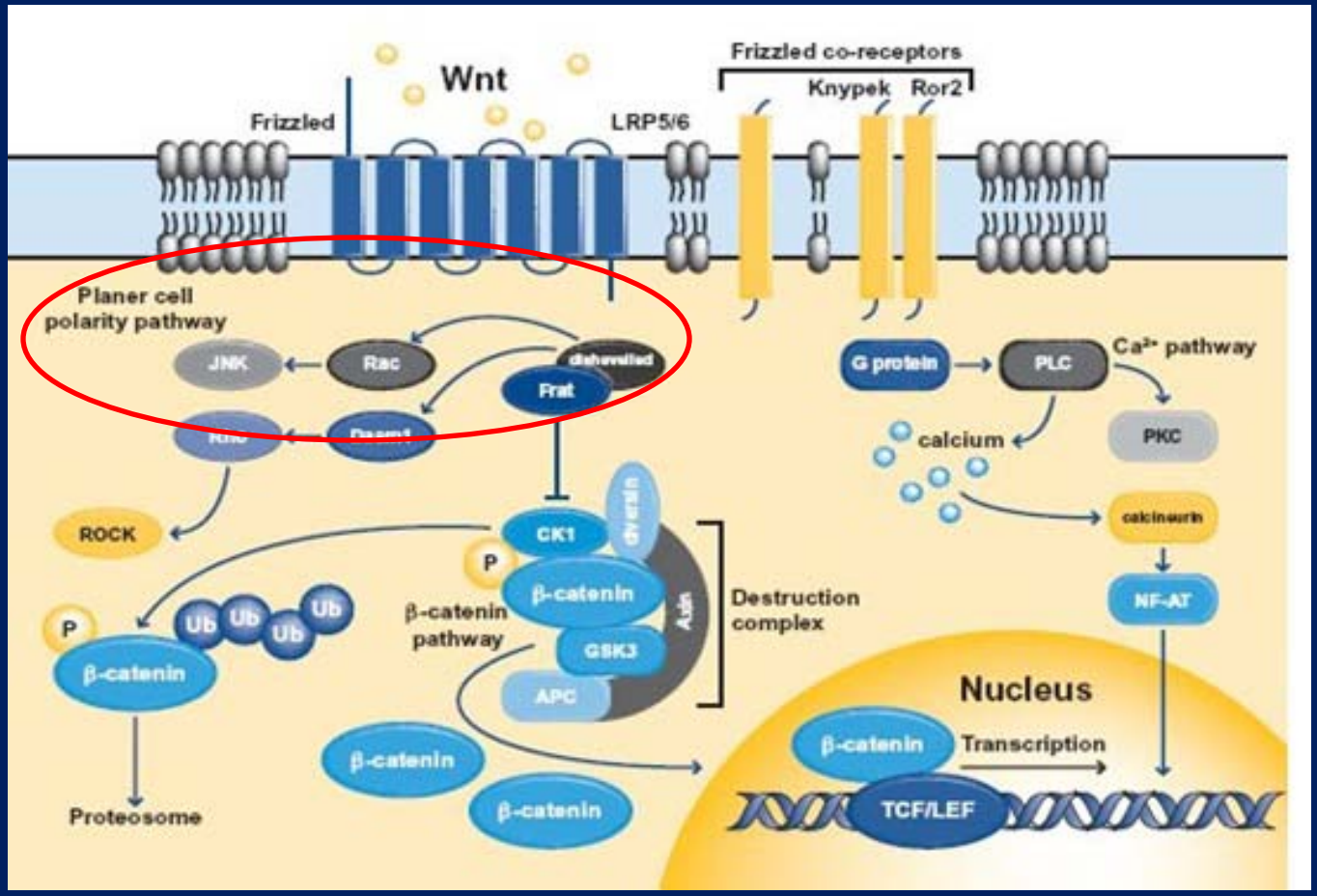
* = LL/PL vs. IL/PL, LL/PL vs. IL/PP, LL/PL vs. LL/PP, $p<0.05$

Discussion

- ANKRD6 genetic variants modulate habitual PA, particularly among women reporting rigorous levels of physical exertion.
- Women with the LL/PL haplotype expend more hr/wk in vigorous PA and more kcal/wk in sports
- Many gene phenotype associations are gender dependent

Discussion

PCP pathway



Implications

- What does this mean?
  - Use of genetic information to develop weight loss and training goals specific to the individual, with ultimate goal of improving PA participation
  - Identify women more likely to participate in rigorous levels of PA

Strengths

- Large homogenous sample
- Multiple SNPs
- Haplotypes

Limitations

- FAMuSS not designed to measure exercise participation
- Young, self-selected sample
- Self-reported data (questionnaire)
- Habitual PA is a complex behavior

Conclusions

- ANKRD6 genetic variants modulate habitual PA, particularly among women participating in rigorous levels of PA.
- Further work is needed to validate our findings and explore the pathways through which ANKRD6 SNPs influence habitual PA.

References

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