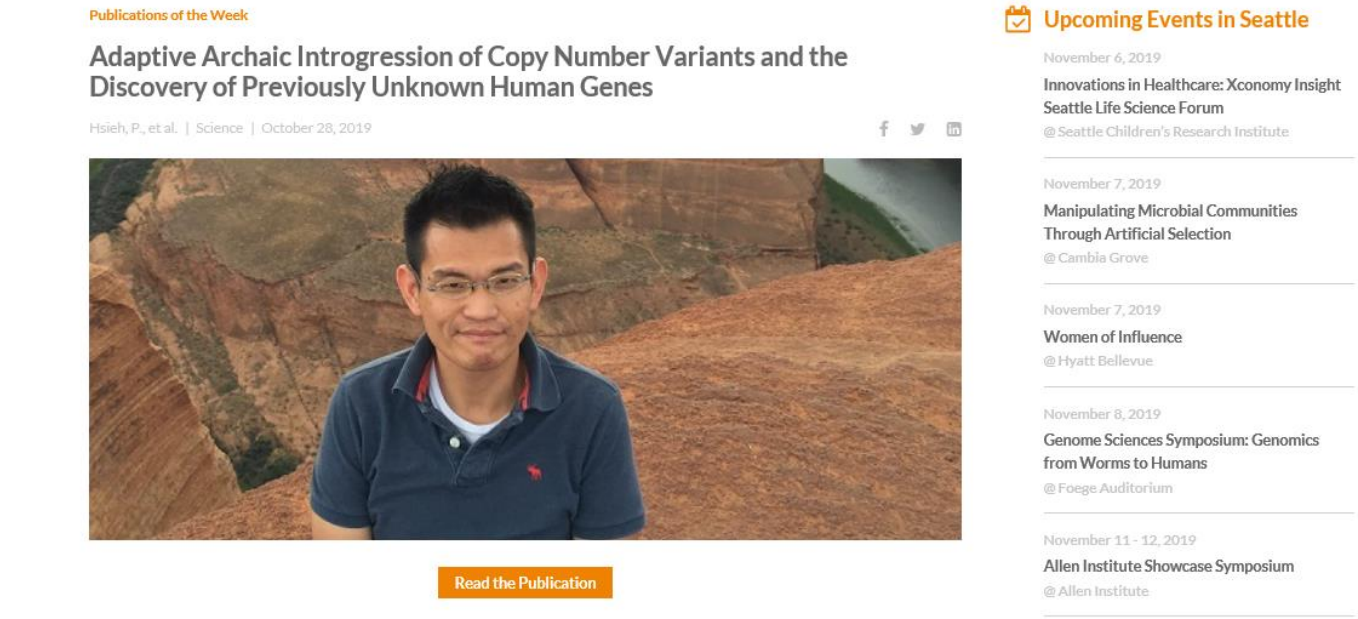

Read the Publication

*This week we profile a recent publication in Science from **Dr. PingHsun (Benson) Hsieh** (pictured) in the laboratory of **Dr. Evan Eichler** at the UW School of Medicine.*

Can you provide a brief overview of your lab's current research focus?

Our lab uses computational and experimental genomic approaches to understand more complex forms of genetic variation, especially recently duplicated regions associated with copy number changes between and within primate species. We use this information, in conjunction with whole genome sequencing data from families, to understand the role that this variation has played in contributing to recurrent rearrangements associated with neurodevelopmental disorders such as autism and intellectual disability. We also investigate the benefits of this form of variation during evolution. Duplications have the potential to create new genes with new functions in species, and recent data suggest that this form of variation has led to the emergence of human-specific genes important in the expansion of the human brain, as well as other features that make us uniquely human.

What is the significance of the findings in this publication?

Genetic hybridization between closely related species is a common phenomenon in nature. Such interbreeding events are particularly important for organisms recently migrating to new environments because they provide an effective means for the newcomers to acquire beneficial genetic materials from the established local species. Using variation patterns of single nucleotide mutations, genetic variants from our now-extinct relatives, such as Neanderthals and Denisovans, have been suggested their roles in the adaptation of modern humans. However, copy number variants

(CNVs) – a type of structural variants resulted from deletions or duplications of large stretches of DNA – are far more likely to affect gene functions but whose adaptive roles in human evolution remains unexplored.

In this study, we systematically searched for CNVs that were likely introduced from archaic humans and show evidence for undergoing positive selection in modern humans. To this end, we designed and performed whole-genome analyses as well as population and comparative genetics inferences. We identified 19 such CNVs in Melanesians, an oceanian population in the Bismarck Archipelago and Bougainville Island, just to the east of New Guinea and known to carry more archaic ancestry (2-4%) than other modern humans. Many of these CNVs encompass genes that are associated with metabolism, cell cycle and development, or immune responses, and thus these findings imply the important roles of these CNVs in the adaptations of Melanesians.

The large adaptive CNVs at chromosomes 16p11.2 and 8p21.3, which were derived from Denisovans and Neanderthals, respectively, are absent from most other human populations. At chromosome 16p11.2, we show that a large duplication of over 383,000 base pairs found more than 79% of Melanesians originated in Denisovans and was introduced into the ancestral Melanesian population 60,000 to 170,000 years ago. On chromosome 8p21.3, we report a Melanesian haplotype carrying two CNVs with a Neanderthal origin was introgressed into non-Africans 40,000 to 120,000 years ago. Using long-read DNA sequencing data, our analysis results show that Melanesians carry new human genes acquired from archaic humans at these two loci and that these new genes are likely beneficial in Melanesians.

These findings are significant for three reasons. We provide some of the first evidence that large copy-number changes that originated in archaic hominins, such as Denisova and Neandertals, have played an important role in helping our ancestors adapt to new environments as they spread out across the globe. Second, we show that these ancient duplications carry duplicated genes that are specific to different human populations and absent in others where ancestral interbreeding did not occur. Third, our results show that human genomes can differ dramatically in sequence content and organization, which justifies the need to build new reference genomes for both studies of disease and evolutionary adaptation.

What are the next steps for this research?

We see two next steps. The first and perhaps most difficult is to identify the phenotypic traits to which these large structural changes are contributing. This is a limitation of the current study but a tall order because these new genes are only found in Melanesians and absent in other humans and organisms. This limits the tools and databases that we can apply to investigate their true function. Ideally, we would be interested in working with local scientists and the research community in Melanesia (eg. Papua New Guinea) to further investigate potential functions of these variants, to assess the origin of their beneficial roles, and to determine if these variants are contributing to or protecting against specific diseases.

Second, we would like to repeat the analysis for additional human populations (eg. Europeans, South Asians) where admixture with archaic species has been predicted. We don't believe this phenomenon is restricted to Melanesians as there is good evidence that single-nucleotide variation has operated similarly (eg. altitude adaptation in Tibetans). The challenge here is that the duplication variants are both complex and enormous when compared to single nucleotide variants. Ironically, hundreds of kilobasepairs of duplicated sequence make them easy to miss by standard sequencing methods. We are therefore working to create new high quality human reference genomes using long-read sequence data which will allow us to sequence and assemble these more complex forms of structural change. We believe that the evolutionary significance of structural variation is insufficiently examined, but is needed to put together a more complete picture of human genome evolution.

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