OSA Phenotypes and Genetics

Definition of the OSA Phenotype

- Definition of OSA Phenotype:
  - Syndrome defined by occurrence of repetitive episodes of complete or partial upper airway obstruction during sleep
- Most family and genetic studies of OSA have used AHI to define phenotype
  - AHI correlated with other indexes of OSA severity like nighttime O2 saturation and sleep fragmentation
  - AHI shows genetic associations
  - Stage-dependent OSA can be genetic too
- Multidimensional phenotypes can give more genetic correlation

OSA Risk Factors

Strong risk factors = Male gender and obesity

Substantial portion of the genetic basis for OSA is independent of obesity genetics

Other risk factors are those that influence upper airway size, ventilatory control mechanisms, and possibly elements of sleep and circadian rhythm control

OSA Risk Factors

- Four primary pathogenic pathways through which genes might act to increase susceptibility to OSA:
  - Obesity and body fat distribution and related metabolic syndrome and inflammatory phenotypes
  - Craniofacial and upper airway morphology
  - Control of ventilation
  - Control of sleep and circadian rhythm

Obesity and Body Fat Distribution

- Obesity increases OSA risk by two- to ten-fold
  - Strongest associations observed in middle age
- Fat deposition may narrow upper airway and predispose it to collapse during sleep
- Fat in thorax and abdomen increase work of breathing, causing hypoventilation and reduced lung volumes, which in turn lead to increased risk of O2 desats
- OSA and obesity appear to be related to genes that operate independently and to others that predispose to both conditions

Craniofacial Morphology

- Predisposes patient to OSA by reducing upper airway dimensions and patency
- See variances in elongation of soft palate, macroglossia, and hypertrophy of tonsils and adenoids
- At least 50 syndromes with congenital malformations of mandibular and maxillary structure
- MRIs have shown that the lateral pharyngeal wall and tongue are larger in OSA patients

Craniofacial Morphology

- Cephalometry shows that OSA patients have reduction of anterior-posterior dimension of the cranial base, increased lower facial height, mandibular retrognathia or micrognathia, and inferior displacement of the hyoid
- Brachycephalic (flattened area at back of skull) head form identifies families at risk for OSA and SIDS
  - Seen more in those of European and Asian ancestry
  - Associated with upper airway narrowing and reduced hypoxic ventilatory responsiveness
- Hard tissue and soft tissue factors predicted AHI level in European Americans
  - In African Americans, soft tissue factors predicted AHI but hard tissue factors were only weakly associated with OSA

Craniofacial Morphology

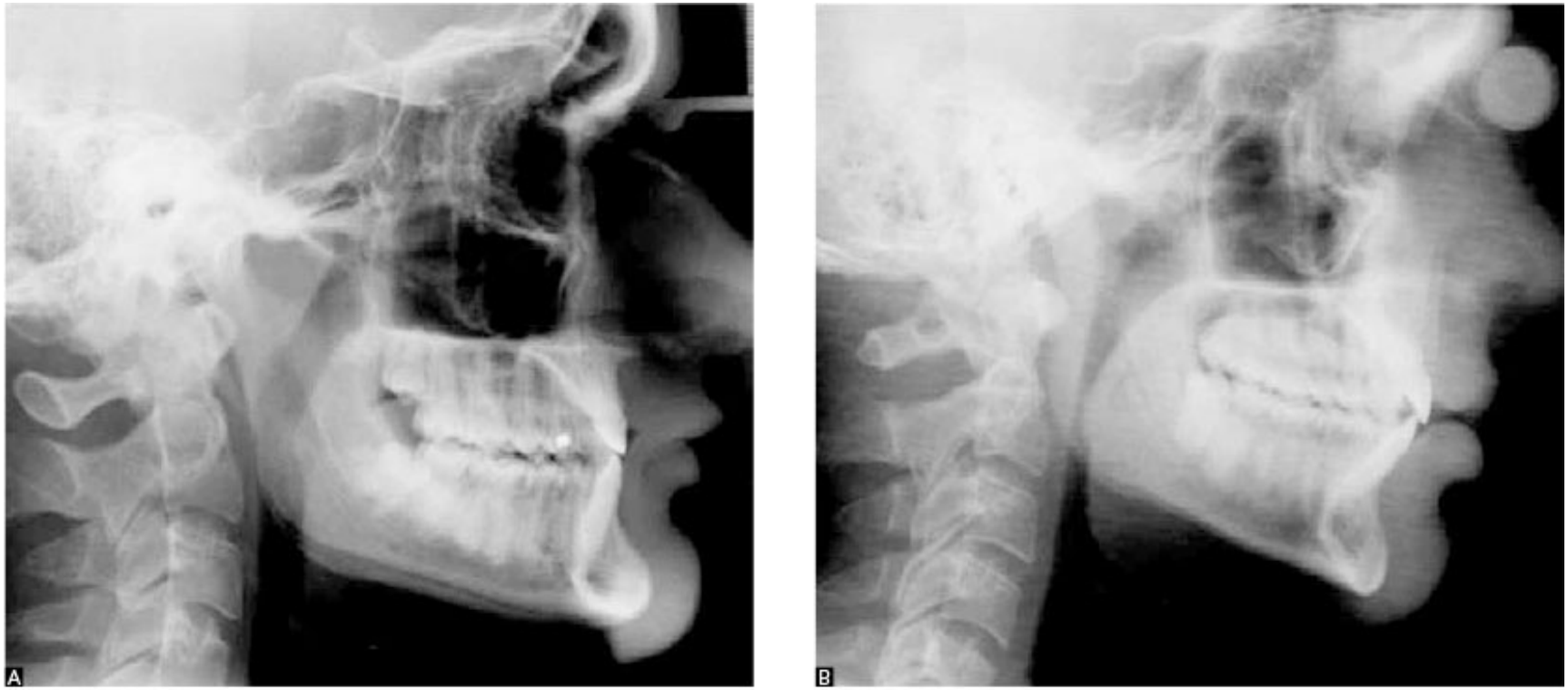

Figure 4 - **A)** Example of radiographs of control group's individual **B)** example of radiographs of OSAHS individuals.

Ventilatory Control

- May include neuromuscular responses to influences of state (sleep-wake), chemical drive, sensitivity of ventilatory load compensation, and arousal threshold
- Variations in the contributions of these factors to OSA

Control of Sleep and Circadian Rhythm

- Abnormalities in orexin genes relevant to OSAH because of potential impact on arousal and muscle tone
  - These neurons are close to the central respiratory control centers
- Orexins play a role in energy homeostasis and regulation of feeding

Familial Aggregation of OSAH

- Have to look at family history
  - Information on snoring, apneas, and sleepiness among first-degree relatives can help determine likelihood of OSA
- Members from families with both OSA and SIDS cases have anatomic features that lead to upper airway narrowing and have reduced hypoxic ventilatory responsiveness
- OSA is transmitted across generations
  - Prevalence of OSA among first-degree relatives is 22-84%

Familial Aggregation of OSAH

- OSA has been described as occurring more commonly as a multiplex (affecting at least two members) than as a simplex (occurring in a single family member) disorder
- Need to gather patient's family history as part of sleep disorder evaluation
  - Especially info on snoring, apneas, and sleepiness among first-degree relatives
- Several studies have shown a correlation between OSA and SIDS and other acute life-threatening events
  - Many of these families have increased prevalence of brachycephaly
- In kids, OSA and adenotonsillar hypertrophy have been elevated in siblings of kids with OSA

Genetic Analyses

- Candidate gene studies = Testing those with same molecular gene characteristics for OSA
- Animal research has shown serotonin influences upper airway reflexes, ventilation, and arousal as well as sleep-wake cycling
- Animal and human studies have shown that leptin has important effects on central ventilatory drive mediated by brainstem receptors in hypercapnic responses
- Genes in inflammatory pathways may contribute to OSA by influencing upper airway patency through effects on pharyngeal edema, tonsillar hypertrophy, and pharyngeal neuropathic changes

Genetic Analyses

- An allele of the apolipoprotein E E4 gene associated with the increased risk for both cardiovascular disease and Alzheimer disease was reported to be associated with OSA in two studies of predominantly Caucasian subjects
- Angiotensin II (vasoconstrictor) may influence ventilatory drive too
  - Correlation with OSA and hypertension

- Linkage analysis and genome-wide association analysis are being performed to identify families at risk for OSA

What Genes Tell Us About Sleep

- https://www.youtube.com/watch?v=e9zuv-NyEx0