Dr. Dominique Hervé, M.D. (CERVCO Hopital Lariboisiere, Paris, France) discussed the wide phenotypic spectrum of motor deficiency and cognitive impairment from executive dysfunction to severe dementia that is observed in CADASIL. Highlighting the cases of two individuals both confirmed as CADASIL on opposite ends of this phenotypic spectrum, Dr. Hervé demonstrated the wide range of symptoms that can be observed: case 1, a 67 YO male with three lacunar infarcts between 51 and 62 yrs, depression, seizures and significant cognitive decline; and case 2, a 71 YO female completely asymptomatic. Both display diffuse lacunar encephalopathy on MRI, however, there were no infarcts nor cerebellar atrophy present on MRI for case 2, demonstrating the importance of lacunar infarct load and cerebellar atrophy in predicting impairment in CADASIL patients.

Viswanathan Anand, M.D., Ph.D. (Massachusetts General Hospital, Boston, MA) presented on the cognitive profile typically seen in symptomatic CADASIL patients, highlighting the case of a 51 yr old man with no known vascular risk factors for stroke, who developed acute left hand clumsiness. MRI revealed lacunar infarcts prompting genetic testing for CADASIL. Despite high-level functioning at the time of his CADASIL diagnosis, neuropsychological evaluation revealed mild deficits in certain areas of attention, verbal learning and memory that require executive functioning. Changes in his personality were prevalent over the years immediately following. Most notably, he became increasingly apathetic towards his family, openly flaunting an extra-marital affair and causing significant stress in his intra-familial relationships. Dr. Anand highlighted the commonality of executive dysfunction in CADASIL, as seen in the represented case, and stressed the correlation between the degree of brain atrophy and CADASIL-associated cognitive impairment and disability.

Using CADASIL as a model for studying structure-function relationship in purely vascular-associated disease, Marco Düring, M.D. (Institute for Stroke and Dementia Research, University of Munich, Germany) talked about new findings on brain imaging in CADASIL. In addition to brain atrophy, lacunar volume and mean diffusivity as independent predictors of cognitive impairment, Dr. Düring’s research points to lesion location as an equally important factor. Utilizing voxel-based lesion-symptom mapping (VLSM), Dr. Düring’s group has shown specific regions in the brain to be directly linked to specific cognitive aspects. For example, lesions in the forceps minor and anterior thalamic radiation predict decreasing processing speeds in CADASIL patients.

Swati Sathe, M.D., M.S., (Division of Neurogenetics, NYU School of Medicine, New York, NY) presented on the various factors involved in diagnostic delay in CADASIL patients. Highlighting issues such as overlapping symptoms between CADASIL and other neurological disease and atypical clinical presentations in CADASIL, Dr. Sathe discussed the difficulties in obtaining early diagnosis. Preliminary data from her group’s natural history study on CADASIL showed an average diagnostic delay from symptom onset to be over 10 years. Factors hypothesized to be major contributors to this delay ranged from CADASIL’s classification as a “rare” disorder to the differing clinical features through each decade of life to the presentation resembling more “common” conditions (i.e. atypical migraine/complicated migraine, MS, vascular dementia and microvascular disease).

Arndt Rolfs, M.D., (University of Rostock, Germany) provided an overview of the SIFAP (Stroke in Young Fabry Patients) project in which 46 international neurologic centers have collaborated in hopes of clarifying the prevalence of Fabry disease in young stroke patients and to characterize stroke rehabilitation in young patients with Fabry disease. The researchers had successfully acquired complete genome sequence data of the NOTCH3 gene on 480 subjects, nine of which showed mutations in the gene. There were no clear CADASIL phenotypes amongst the nine subjects, and eight of the variations detected on sequencing were of undetermined biological consequence. All nine did, however, display a high rate of positive family history and recurrence of stroke.
**Mrs. Billie Duncan-Smith** (CADASIL: Together We Have Hope Foundation, Roundrock, TX) discussed her and her family’s experiences in dealing with CADASIL and the circumstances that lead to her founding of the CADASIL: Together We Have Hope Foundation in 2005. The various tools and information available through the foundation’s website were presented as well as data acquired through the foundation’s registry such as demographics and frequency of reported symptoms. These data were further analyzed and broken down by specific symptoms and their correlation to specific demographics. Ms. Duncan-Smith finished her talk with a detailed overview of her family’s pedigree as related to CADASIL and its inheritance.

**David Knopman, M.D.,** (Dept of Neurology, Mayo Clinic, Rochester, MN) discussed the high prevalence of cerebrovascular disease in elderly populations, specifically looking at the impact it has on dementia. Dr. Knopman highlighted contributing factors towards the confounding interpretations of CVD in dementia and why it is sometimes dismissed as a contributing element towards cognitive impairment in the elderly. As CVD is typically a result of lifelong exposure to risk factors for athero/arteriosclerosis, Dr. Knopman proposes that CVD be viewed as an important, but not major contributor to cognitive impairment late in life. Most importantly, if the CVD burden is modifiable at the mid-life stage and can be reduced, then the weight of late-life dementia may also be reduced.

**Raphael Schiffmann, M.D.,** (Baylor Research Institute, Dallas, TX) talked about Fabry disease as a model for genetic vasculopathies, specifically highlighting its relevance to CADASIL. Each genetic vasculopathy has a unique profile and mechanism, and it is the study of these profiles and mechanisms that are most crucial to the development of specific therapies. Lastly, Dr. Shiffmann advised to beware of all dogmas traditionally associated with genetic vasculopathies as research continually proves many previously held beliefs to be unclear.

**Kathryn Gardner, M.D.,** (Veteran’s Administration, University of Pittsburgh, Pittsburgh, PA) presented an electrical paradigm as a way to determine which signaling pathways are shared amongst monogenic disorders associated with migraine. Starting with the most highly-elucidated pathway (calcium channel pathway) data in the model organism *C. elegans* and comparing that with previously established data on humans, Dr. Gardner’s team has annotated large amounts of data on these pathways and their importance in migraine associated disease. Additionally, recent findings on the synergistic relationship between Notch and TGF-β signaling in smooth muscle cell modeling were presented.

Utilizing *in vitro* and *in vivo* based experiments in mouse and human models, **Anne Joutel, M.D.,** (INSERM, Paris, France) and her group works diligently to elucidate the origin, development and effects of CADASIL in affected individuals. Critical findings presented by Dr. Joutel includes the vascular smooth muscle cells lining small arteries and pericytes of capillaries as the primary target cells in Notch3 expression, making CADASIL a small-vessel disorder. The physiological role of Notch3 in the vessel, significance of CADASIL mutations and mechanisms of specific brain lesions were discussed, as well as implications for therapeutic trials. Most notably, Dr. Joutel proposes that it is due to a novel pathogenic role for mutant Notch3 as cause for CADASIL as opposed to loss or gain of function.

**Luisa Luella Arispe , M.D.,** (UCLA Los Angeles, CA) is a vascular biologist performing research on the regulatory pathways most important in orchestrating blood vessel development in mammals. Highlighting the interplay of Notch and Jagged in the walls of adult vessels, Ms. Arispe discussed the circuitry of signaling that takes place and the importance in evaluating the constellation of interactions taking place between these pathways in understand disease.

**Michael Wang, M.D.,** (VA Medical Center at University of Michigan, Ann Arbor, MI) presented research his group is doing on Notch3 signaling and binding proteins and how his group’s findings may correlate to CADASIL. The group concluded that Notch3 signaling can be regulated by adapter proteins (e.g. TSP2) and established the function of Notch3 to be coupled to endocytosis of the protein, as in Notch1. In an LRP1 endocytic-protein-associated mechanism, TSP2 binds to and enhances the activity of Notch3. TSP2 fragments may therefore stimulate endocytosis of the Notch3 ectodomain. These findings suggest that establishing new pathways for Notch3 clearance could prove useful in creating therapeutic treatments for CADASIL.
Employing SIFT methods for single-particle analysis of Notch3 multimerization, Marco Düring, M.D., (Institute for Stroke and Dementia Research, University of Munich, Germany) and his research group has characterized the aggregation of Notch3 protein in vitro. They found that CADASIL-mutations in the Notch3 gene lead to enhanced Notch3 multimer quantity, only mutant multimers display fluorescent resonance energy transfer (FRET) qualities, cysteine residues are most crucial and that hetero-multimer formation is possible. Moving forward, Dr. Düring and his group plan to investigate as to whether or not these aggregate interactions can be replicated in vivo, if there is a link to cell degeneration and if anti-aggregatory compounds can be developed as possible therapy.

Utilizing transgenic mice, Katarina Elkermann-Haerter, M.D., (Massachusetts General Hospital, Boston, MA) research aims to describe the phenotypic presentation of migraine and stroke arising from mutations in the Notch3 gene. In reference to the migraine phenotype, Notch3 mutations increase susceptibility to cortical spreading depression. Regarding the stroke phenotype, susceptibility to peri-infarct depolarization was increased, as well as, increased risk for cerebral blood flow deficits, larger infarct size and enhanced neurological deficits, despite “normal” cerebrovascular anatomy at the microscopic level. Overall, their research suggests that vascular mutations in the Notch3 gene increase the likelihood of cortical spreading depression and ischemic depolarization; both mechanisms may be responsible for migraine and stroke phenotypes observed in CADASIL.

Dominique Hervé, M.D. (CERVEO Hopital Lariboisiere, Paris, France) began his second presentation speaking to the importance of psychological support for CADASIL patients and their family after diagnosis in order to combat the psychological consequences implicit with receiving the diagnosis, even in the absence of severe symptoms. Genetic counseling is also an important component of this psychological support. Dr. Hervé went on to discuss recommendations for daily management, citing treatment with the standard array of prophylaxis for vascular risk factors (i.e. anti-HTN meds, statins, etc.), as well as, treatment of migraine and mood disturbances. As the disease reaches the more advanced stages, rehabilitation to improve functional independence, nursing care and social support become increasingly important.

James Galvin, M.D., (NYU School of Medicine, New York, NY) began his talk with an overview of the clinical manifestations seen in CADASIL, highlighting the enormous burden caused predominantly by behavioral and psychological symptoms of dementia (BPSD) in the latter stages of the disease. An increasingly common tool of measurement of this is the Neuropsychiatric Inventory (NPI). Dr. Galvin stressed the importance of diagnosing and evaluating psychiatric disturbances in CADASIL patients, of which depression and apathy are most prevalent, as their treatment may improve quality of life. In addition, psychiatric manifestations may also be representative of the onset of CADASIL, especially in young patients, and should thus be included in the differential diagnosis. Dr. Galvin recommends treatment with SSRI antidepressants as the first line of therapy, supplemented by an atypical antipsychotic as needed. Non-pharmacological approaches should also be considered, and the general rules to follow regarding treatment of these disturbances are, “start low, go slow” and “re-assess, re-evaluate and repeat.”

Sonia Reyes, a psychologist from France, discussed their protocol of testing individuals at risk for CADASIL due to family history. The protocol takes in to account several aspects of pre-symptomatic screening such as autonomy, risk versus benefit of testing, confidentiality and equal access to results. Since most individuals seeking testing are asymptomatic, the team has to establish that the individual has adequate knowledge about the condition and counsel them on potential outcomes. The individual meets with an interdisciplinary team including a neurologist, psychologist and geneticist, followed by a waiting period of two months. The neurologist will then meet the patient again and blood is drawn if the individual still wishes to get tested. The test result is disclosed during a third meeting with both neurologist and psychologist, with post-test counseling and psychological support offered. Due to this rigorous protocol only 33 individuals have chosen to get tested in the past seven years at the Paris Center.