EVA: Exome Variation Analyzer
A tool for filtering strategies in medical genomics

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Exome sequencing is transforming disease gene identification by allowing the discovery of causal genetic variations in Mendelian diseases as well as somatic variants in cancer. But identifying the pathogenic mutations among tens of thousands per individual is a major challenge, and efficient prioritization strategies are required. EVA is a web application developed to be a user-friendly, versatile, and efficient-filtering assisting software for exome sequencing [1]. It constitutes a platform for data storage and for drastic screening of clinical relevant variations by non-programmer medical geneticists. Thereby, EVA provides a response to the need of new bioinformatics tools for medical genomics more and more investigated by targeted NGS technology, for disease research, clinical diagnostics and personalized medecine.

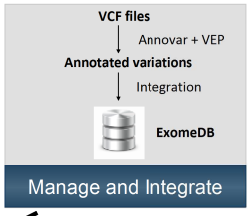
EVA — Exome Variation Analyzer

Manage | Table Browser | Quick Search | Filtering Strategies | Variation statistics | Ressources

Overview of the functional modules

For a given exome project corresponding to several individuals, EVA allows to analyse and filter data through different modules, as strictly confidential to the project owner.

The **Variation Integration module** takes in input standard raw Variant Call Format files, and annotates the variations thanks to Annovar and the Variation Effect Predictor EnsEmbl API. Annotated variations are then stored in a database called **ExomeDB.**



Manage and Integrate

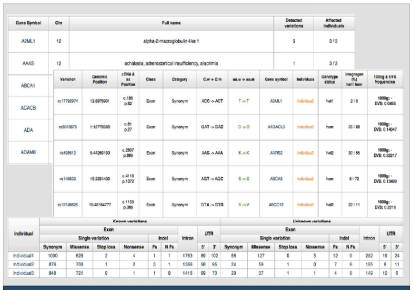
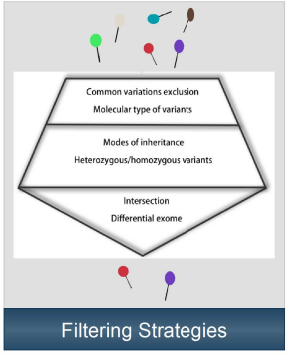


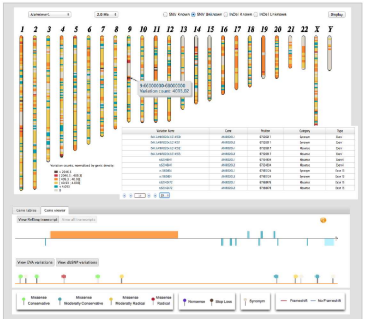
Table Browser

The **Table Browser module** allows to explore exome data by project, individual, gene or annotated variation through sortable and interactive tables.



Filtering Strategies

The **Filtering strategies module** proposes to combine multiple current filters to drastically narrow down variations. Remaining variations are displayed in tables format.



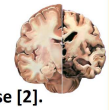
Quick Search

The **Quick Search module** offers a direct access to a gene or a variation for a given project. It also provides interactive graphical views : a **caryotypic distribution of variations** allowing a focus on the variations of a selected region, and a **graphical gene view** for the reference and alternative transcripts. A selected exon is displayed with its variations. A selected variation offers text details and a connection to the Table Browser.

Variation Statistics

The **Variation Statistics module** allows to display SNV and indel categories bar charts and pie charts, transition/transversion matrix and amino-acid substitution matrix with Grantham classes. It can be done for all the variations corresponding to a project or for a selection of individuals, chromosomes, regions or genes. Graphics are associated with variation table details.

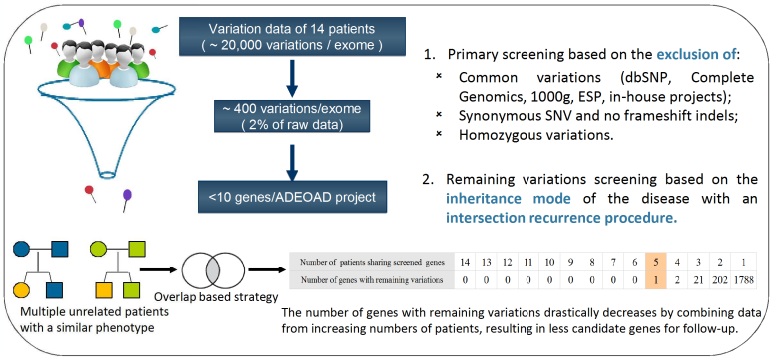
Case study: Alzheimer Disease



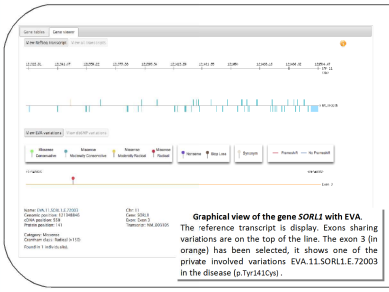
EVA has been used to successfully identify a new gene for a rare Mendelian disease [2].

Whole exome sequencing was performed in fourteen Autosomal Dominant Early-Onset Alzheimer Disease (ADEOAD) unrelated index cases without mutation on involved known genes (*APP, PSEN1* and PSEN2) and also without known copy number variants of *APP* gene or genes involved in Amyloid beta peptide processing or signaling.

Filtering strategy with EVA



Further prioritization of the short list of genes (<10)

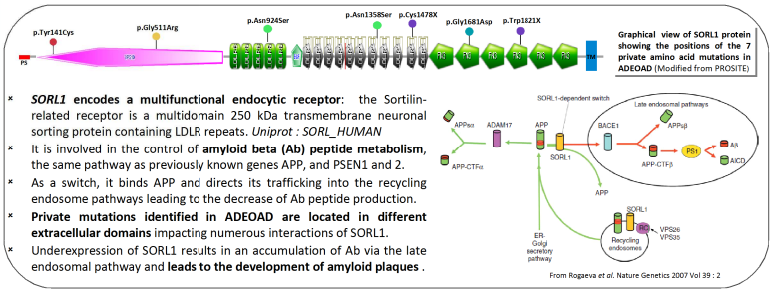


× *In silico* prioritization with other softwares for pathogenic effects inspection of the variations;

× Wet experiments with Sanger resequencing, family cosegregation analysis, genotyping of 1500 individual controls by Chip, RT-PCR analysis.

Conclusion: In 5 exomes/14, the top scoring gene *SORL1*, harboring private nonsense (n=1) or missense (n=4) pathogenic mutations, has become a **new strong candidate gene related to the rare form of Alzeihmer Disease (ADEOAD)**, despite a genetics heterogeneity. Replication sample (15 additional index cases) confirmed this result and allowed to find two more private mutations (one missense and one nonsense).

SORL1: a new candidate for a rare early form of Alzeihmer Disease



× ***SORL1* encodes a multifunctional endocytic receptor**: the Sortilin-related receptor is a multidomain 250 kDa transmembrane neuronal sorting protein containing LDLR repeats. *Uniprot : SORL_HUMAN*

× It is involved in the control of **amyloid beta (Ab) peptide metabolism**, the same pathway as previously known genes APP, and PSEN1 and 2.

× As a switch, it binds APP and directs its trafficking into the recycling endosome pathways leading to the decrease of Ab peptide production.

× **Private mutations identified in ADEOAD are located in different extracellular domains** impacting numerous interactions of SORL1.

× Underexpression of SORL1 results in an accumulation of Ab via the late endosomal pathway and **leads to the development of amyloid plaques** .

References

[1] S. Coutant, C. Cabot, A. Lefebvre, M. Léonard, E.Prieur-Gaston, D. Campion, T. Lecroq, H. Dauchel. EVA: Exome Variation Analyzer, an efficient and versatile tool for filtering strategies in medical genomics. BMC Bioinformatics 2012, in press.

[2] C. Pottier, D. Hannequin, S. Coutant, A. Rovelet-Lecrux, D. Wallon, S. Rousseau, S. Legallic, C. Paquet, S. Bombois, J. Pariente, C. Thomas-Anterion, A. Michon, B. Croisile, F. Etcharry-Bouyx, C. Berr, J.-F. Dartigues, P. Amouyel, H. Dauchel, C. Boutoleau-Bretonnière, C. Thauvin, T. Frebourg, J.-C. Lambert, D. Campion, collaborators PHRC GMAJ, High frequency of potentially causative SORL1 mutations in autosomal dominant early-onset Alzheimer disease. Mol. Psychiatry 2012, AOP, 3 April 2012: doi:10.1038/mp.2012.15.