Conclusion

These results represent a structured and comprehensive analysis of a large patient cohort with mutations in the LEPR. LEPR-deficiency is a serious disease characterized by severe early-onset obesity, hyperglycemia and hypogonadotropic hypogonadism. Further, there is a heterogeneous disease spectrum concerning e.g. infections, growth, development and type 2 diabetes. Till now, we were not able to reveal a genotype-phenotype-correlation. Based on provided information about functional analysis, mutation size, and location, as well as phenotypic characteristics of affected patients we suggest residual function failure in 6 mutations. Future in vitro analysis should confirm this findings.

Objectives

In this project we aimed to summarize published and unpublished functional and phenotypic data on mutations in the human leptin receptor (LEPR) gene causing a rare form of severe early-onset obesity. Further, we estimated the functional relevance of described mutations in the human LEPR and we investigated a possible genotype-phenotype-correlation.

Methods

Literature research was performed using PubMed and OMM. Additional data was obtained from 6 subjects of our outpatient clinic not reported so far. Functional relevance of mutations was estimated based on reported functional analysis, mutation size, and location, as well as phenotypic characteristics of affected patients.

Results

In total 57 subjects with 38 distinct mutations in the LEPR were identified. From 38 mutations, 13 led to a single amino acid change. 25 deletions, duplications, insertions or nonsense mutations resulted in truncated LEPR proteins (Table 1a & Figure 1). In silico analysis were performed for 23 mutations. Functional data from in vitro experiments were available for 4 mutations, showing residual function in one. Considering clinical phenotype and character of respective mutations, we suspect residual function in 5 additional mutations (Table 1b). Summarizing clinical data, we found severe early-onset obesity, hyperglycemia, and hypogonadotropic hypogonadism as cardinal features of a complete loss of LEPR function. Other disease e.g. metabolic disorders and recurring infections were more variable in manifestation. Median body fat percentage and z-score were slightly higher in female compared to male (Figure 2A & B), but comparison is limited due to differences in age and methodology. We found a wide range between the reported LEPR serum concentrations in subjects with LEPR deficiency. This might in part be attributable to assay variability. In addition, truncating LEPR mutations leading to a loss of the LEPR like protein (as in p.W664R & p.T711N) result in highly elevated serum leptin concentrations (measured as bound or total leptin) (Rf).

Using the published values, LEP concentrations and body fat percentage seem to correlate stronger in females than in males. Also, this comparison is limited by the large age differences between the groups (Figure 2D and E). Standardized analytical methods are needed for qualitative statements about LEP concentration in LEPR deficient subjects.

Table 1a: Overview of mutations in the human LEPR (case ID). First author and year of the publication, number of cases, location of the mutated in the LEPR protein, and affected domain. Table 1b: Estimation of the functional relevance of the respective mutations were made based on clinical phenotype, in silico functional data and in vitro functional data. (in vitro visualization of truncated receptor proteins via flow cytometry) (IVD = in vitro domain, 1 - highly relevant, 2 - relevant, 3 - doubtful, 4 - not relevant).

Table 1b: Estimation of functional relevance of the respective mutations were made based on clinical phenotype, in silico functional data and in vitro functional data. (in vitro visualization of truncated receptor proteins via flow cytometry) (IVD = in vitro domain, 1 - highly relevant, 2 - relevant, 3 - doubtful, 4 - not relevant).

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Disclosure Statement

The authors have no conflicts of interest.