

Brain-lung-thyroid syndrome - clinical update on a heterogeneous disorder

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Background

- Brain-lung-thyroid syndrome (BLTS, OMIM# 610978) is caused by mutations in the NK2 homeobox 2 (NKX2-1; TTF1) gene affecting 3 NKX2-1 expressing organs brain, lung and thyroid.
- The syndrome is characterized by benign hereditary chorea (BHC), infant respiratory distress syndrome (IRDS) and congenital hypothyroidism (CH). However, the clinical spectrum and severity of symptoms vary widely.
- Regarding the increasing number of published mutations and heterogeneous phenotypes, a clinical synopsis is needed. Further, genotype-phenotype correlation should be investigated for potential predictability of organ involvement.

Methods

- We performed a systematic review of literature in MEDLINE and EMBASE. All patients with proven NKX2-1 mutations and description of symptoms were included.
- For genotype-phenotype association studies, we compared different mutationtypes and functional domains of the protein with specific phenotypes by Pearson's chi-square test.
- The NMR described structure of the Drosophila NK-2 (PDB accession code 1NK2) and the rat NKX2-1 (PDB accession code 1FTT) were used as templates to build a structure of the human NKX2-1 homeodomain bound to its cognate DNA (homology modelling done with MODELLER software package 9)

Objectives: 1. Summarizing all available cases of NKX2-1 related disorders to provide a detailed clinical overview of BLTS.
2. Performing systematic genotype-phenotype association studies.

Results

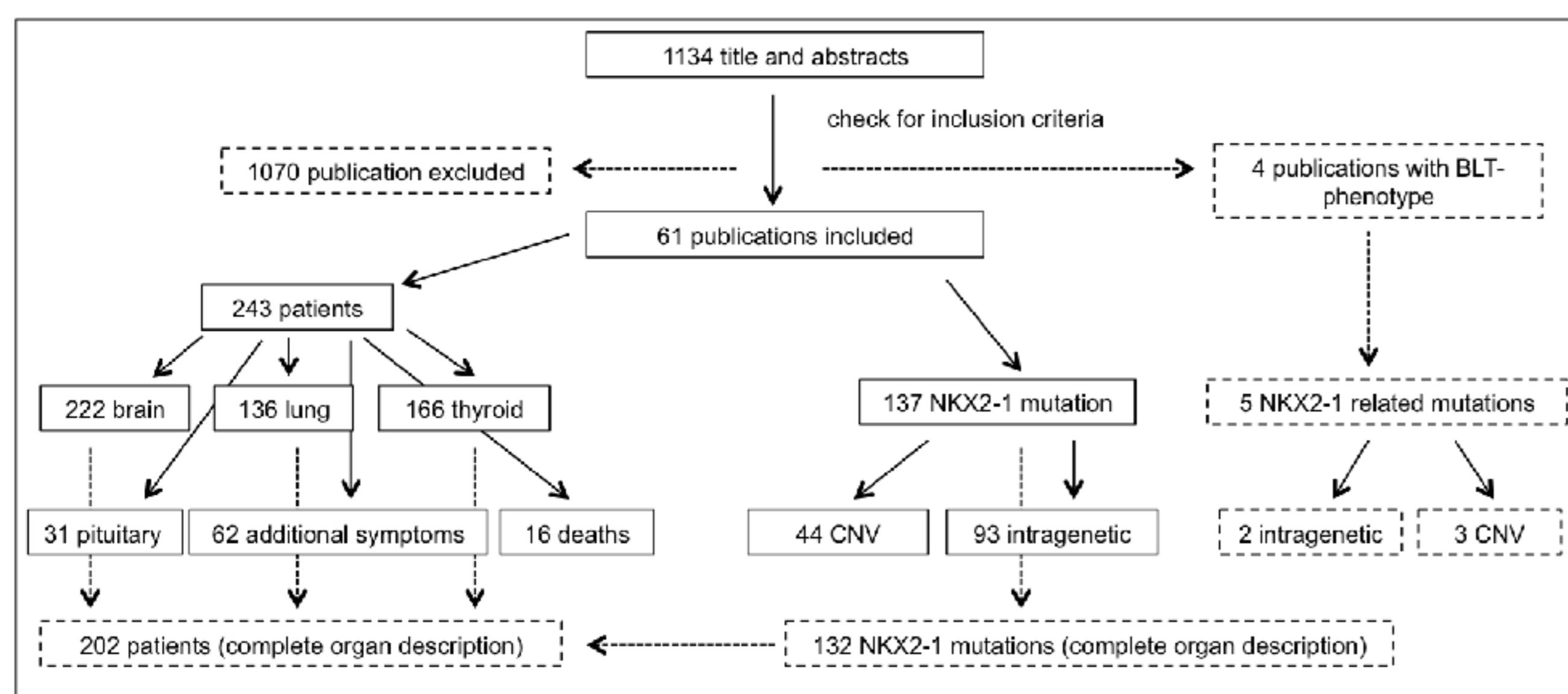


Fig. 1: Study flow chart and overview of patients and mutations.

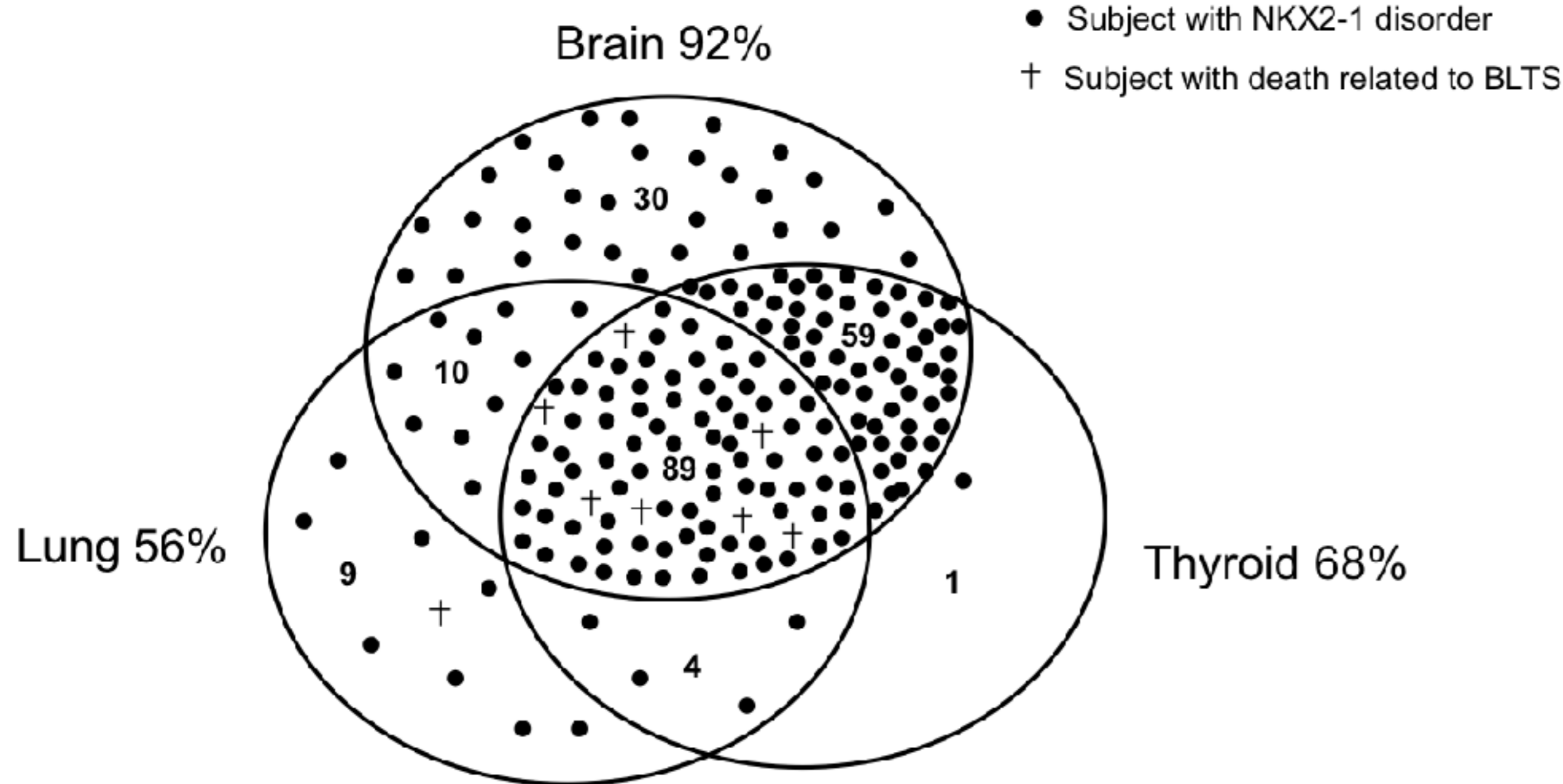


Fig. 2: Spectrum of phenotypes in 202 patients with NKX2-1 mutation and complete description of all 3 organs.

Only 44% suffered from the complete triad of BLTS. 20% showed only one organ involvement.

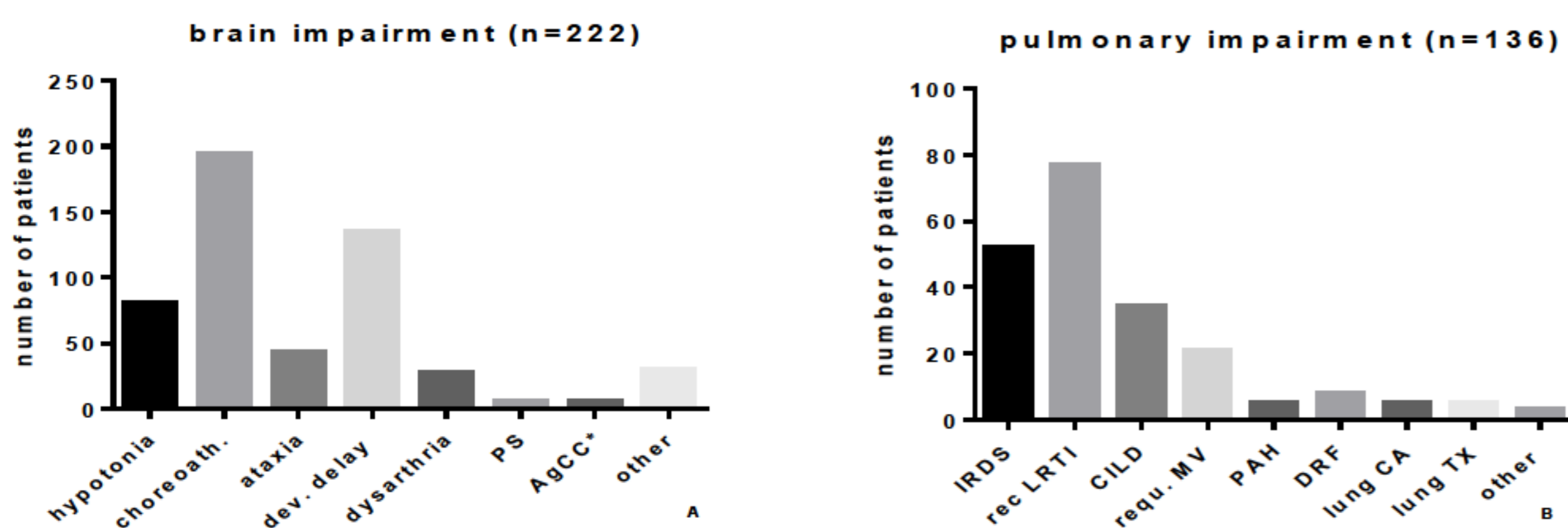


Fig. 3: Overview of different symptoms and signs in the 243 reported patients. **3A:** PS= pyramidal symptoms, AgCC: corpus callosum agenesis (MRI) **3B:** Requ. MV= required mechanical ventilation. PAH= pulmonary arterial hypertension. DRF= Death from respiratory failure.

BHC is the most specific neurologic sign and should rise suspicion of BLTS in either combination of further signs and symptoms. Lung disease is associated with high mortality.

We identified 243 patients with 137 different mutations (Fig. 1). In 202 patients, information on all 3 organs was available for phenotype analysis: Only 44% suffered from the complete triad of BLTS (Fig. 2). Different reported symptoms and signs and their frequency are summarized in Fig. 3 and 4. Only 60% of patients with CH were detected by neonatal screening (mean TSH 130 mU/L), while 40% were diagnosed later (mean TSH 29 mU/L). In a detailed genotype-phenotype analysis, we found a correlation between isolated lung-phenotype and isolated affection of the homeodomain (HD) of the gene ($p < 0.001$), all interacting with the minor groove of its cognate DNA ($p < 0.001$). The HD-region of NKX2-1 with the amino acids of interest are illustrated in Fig.5.

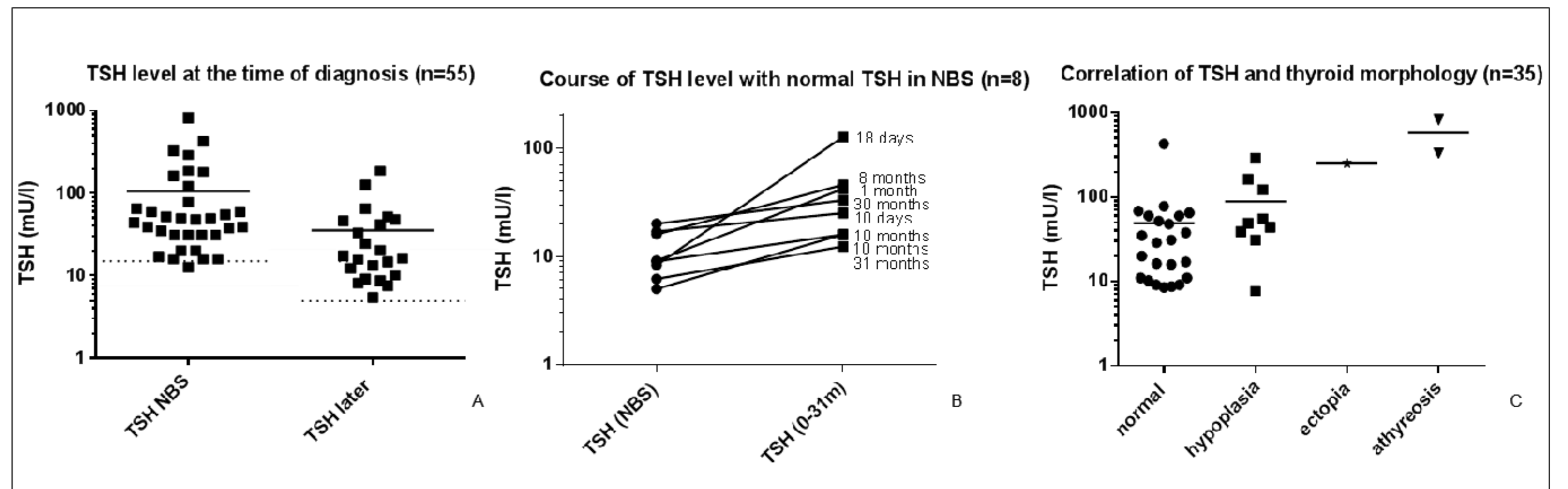


Fig. 4: TSH level in patients with CH. **4A:** Initial TSH level at the time of diagnosis: Newborn screening (NBS) ($n=33$) compared to later diagnosis ($n=22$). **4B:** Course of TSH level in 8 patient with CH but normal TSH at NBS according to local screening cut off (max. 20 mU/ml). **4C:** TSH at diagnosis in correlation with thyroid morphology in ultrasound. * Patient had documented lingual thyroid ectopia and TSH was reported >200 mU/L.

40% of patients with congenital hypothyroidism were not detected by neonatal screening, but only after the neonatal period.

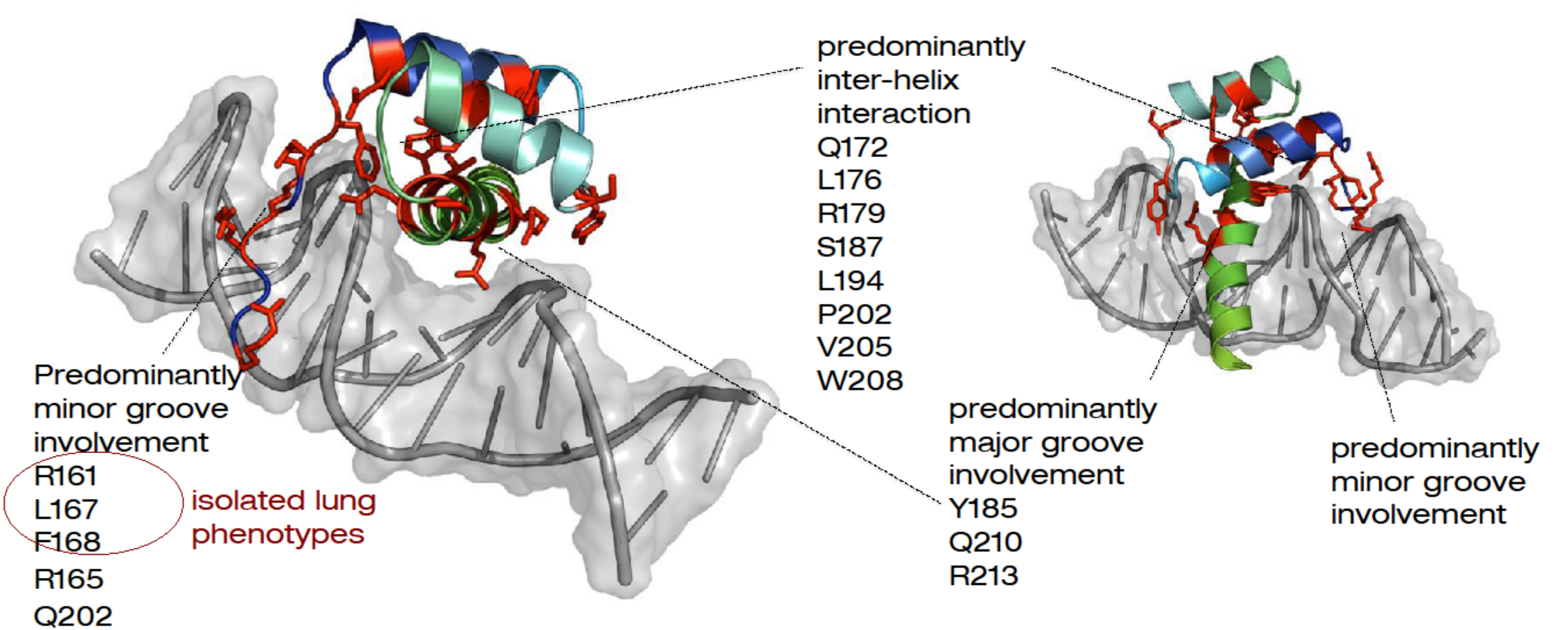


Fig. 5: Homology models of the wild-type homeodomain region of NK2-1 bound to its cognate DNA. DNA structure and its surface are depicted in grey. Amino acid where point mutations have been described are shown in red. The pictures were produced with the PyMOL molecular graphics system (<http://www.pymol.org>).

Isolated lung phenotype is associated with isolated affection of the HD of NKX2-1, interacting with the minor groove of its cognate DNA ($p < 0.001$).

Conclusion

We provide a detailed clinical and genetic overview of BLTS. This study gives new insights in the wide clinical spectrum of the syndrome and shows evidence for potential genotype-phenotype correlation. This knowledge is important for all involved specialists to be aware of NKX2-1 related disorders, even if classical triad is absent. Thus, clinical phenotype of BLTS can be very heterogeneous.

