The role of Anticipation in the incidence of CJD with the Mutation E200K

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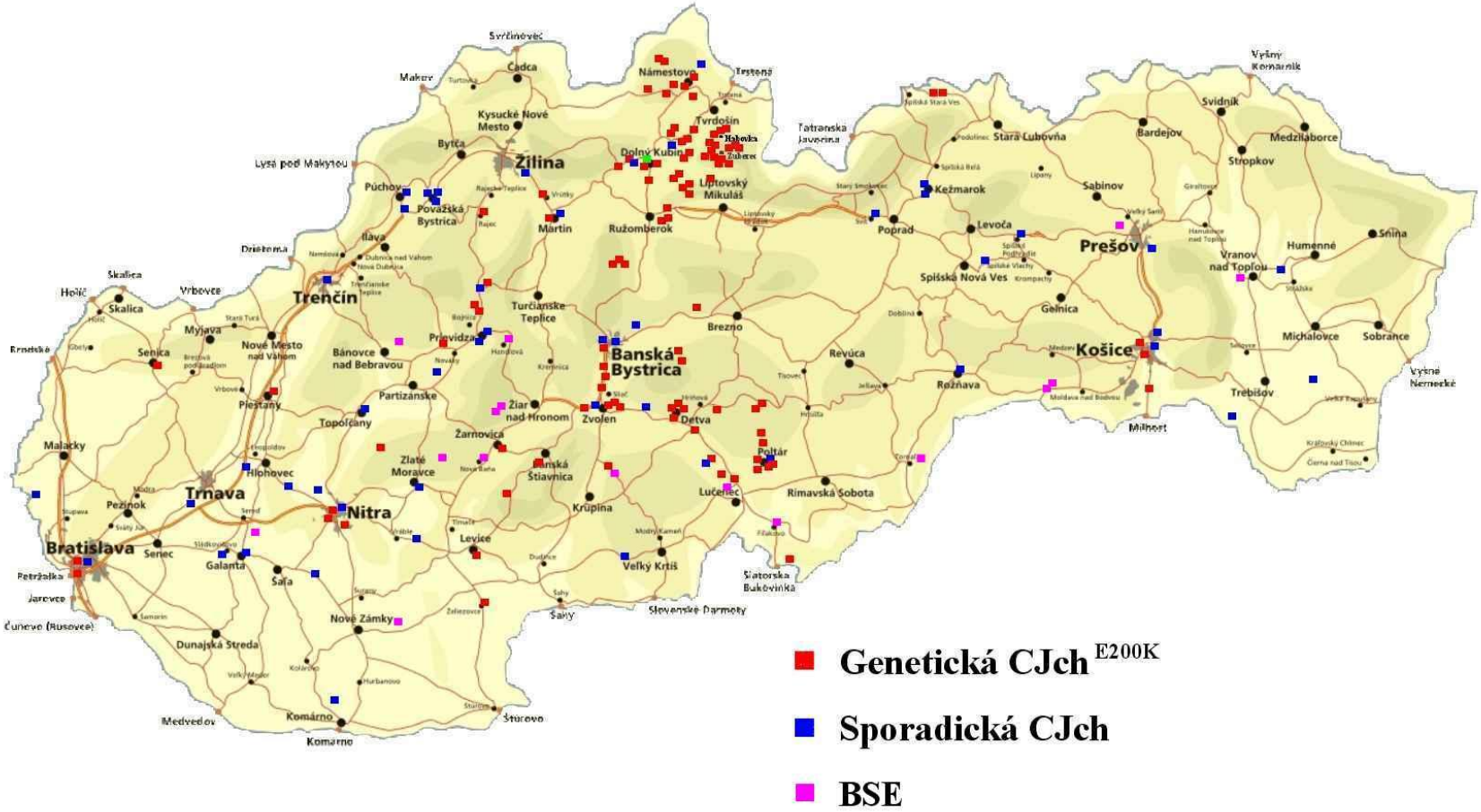
A short retrospective summary .....

The history of Slovak familial CJD^{E200K} started in Orava

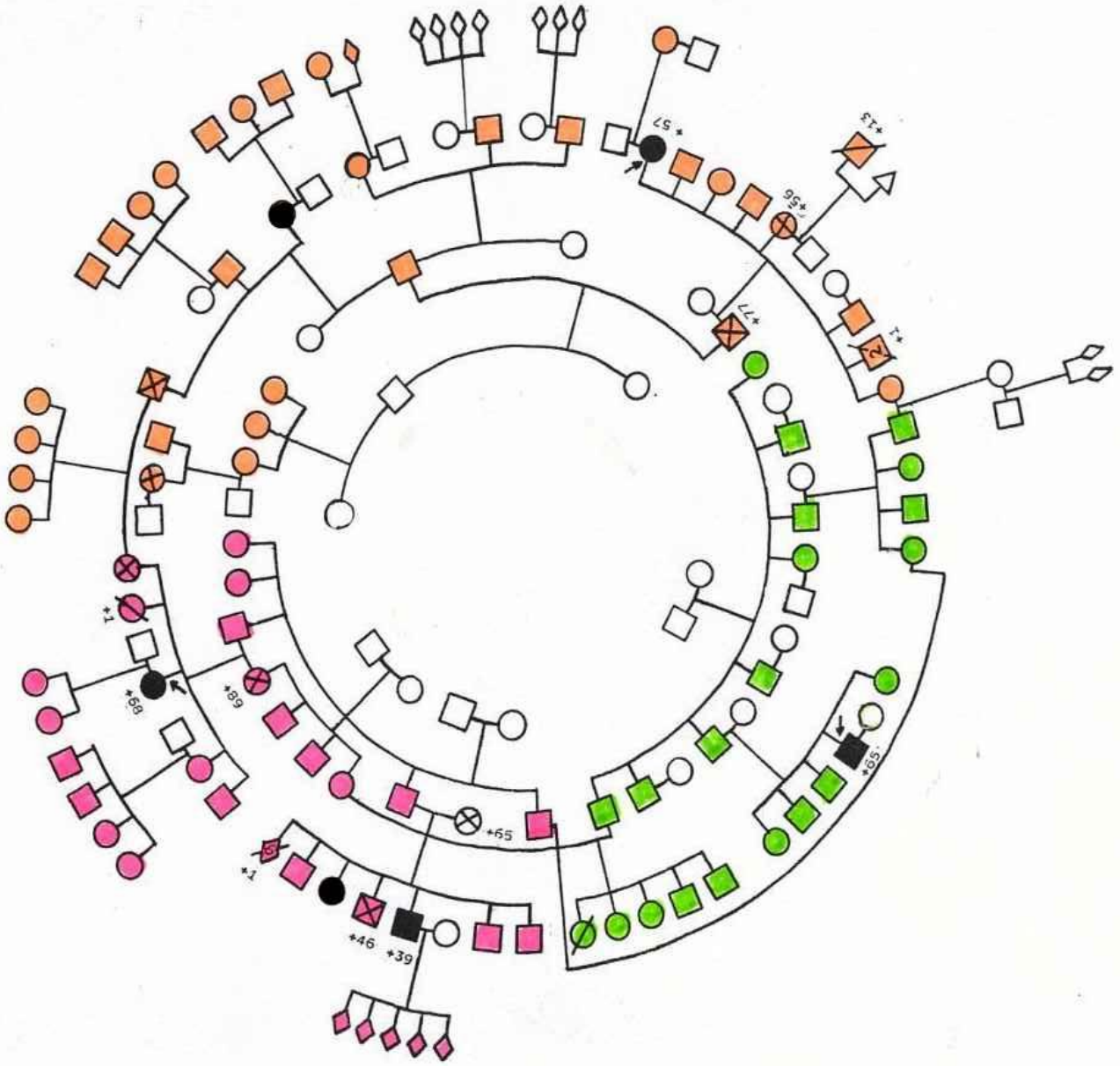
Geographical distribution of CJD according to the birthplace. CJD cluster in Orava



Focal accumulation (cluster) of CJD in Orava had two possible explanations :

1. **exogenous risk :**
   - **study on environmental factors**
   - **zoonotic risk**

2. **endogenous (genetic) risk :**
   - **epidemiological analyses (familial cases)**
   - **genealogical studies**


*57
*56
*43
*77
*1
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*68
*89
*65
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*46
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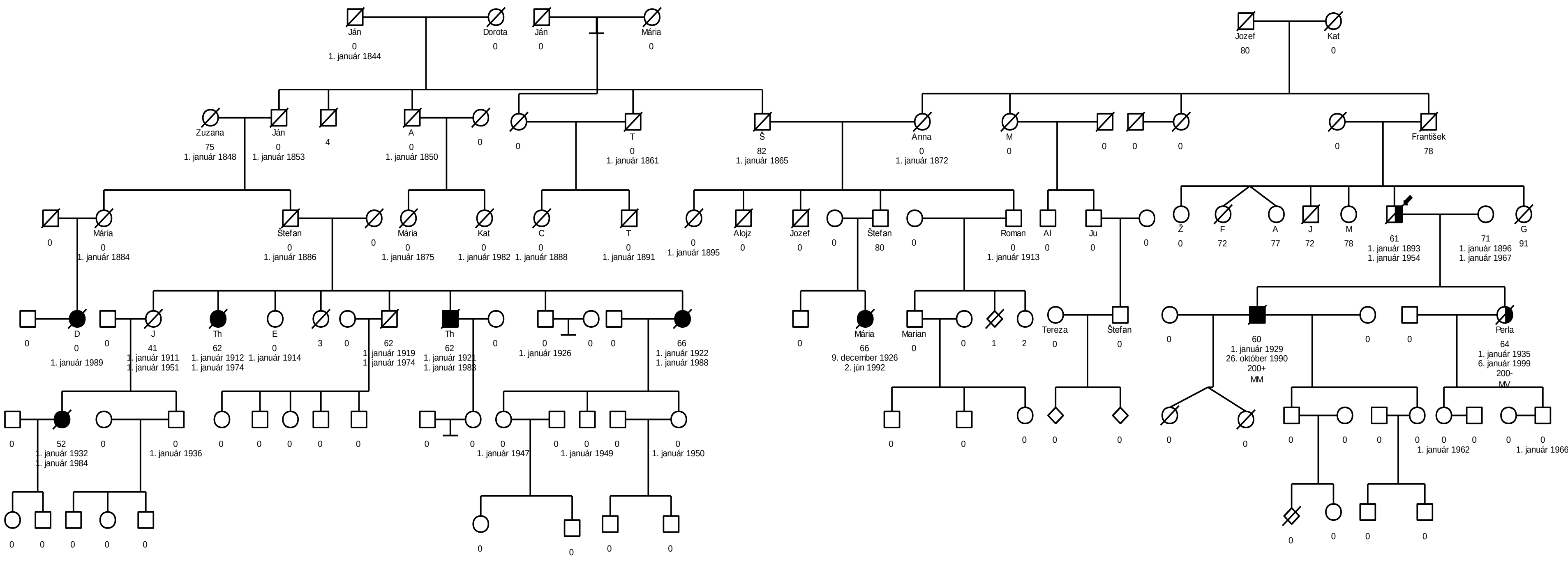
*65

Family Or.


Ján
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1. január 1844
Dorota
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Jozef
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Zuzana
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Ján
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1. január 1850
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1. január 1861
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1. január 1865
Anna
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František
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9. december 1926
2. jún 1992
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Tereza
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1. január 1929
26. október 1990
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Perla
64
1. január 1935
6. január 1999
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52
1. január 1932
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1. január 1947
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Result of epidemiological /genealogical studies in CJD cluster show high percentage of familial cases.

- **Slovak CJD cluster 32% (Mitrová, 1986)**

- **World wide occurrence : 14-15% (Masters et al. 1979)**
- **Chile 26% (Galvez et al. 1979**
- **Israel 25,5% (Kahana et al.1979)**

Introduction of molecular genetic methods :

Prion protein gene< Mutations (insertions/deletions)

V

Genetic TSEs /CJD

All familial cases have mutation,

not all (47%) patients with mutation are familial !!! (sporadic-like genetic cases)

Genetic TSEs patients

Kovács G.et al. 2005 : Genetic TSEs : EUROCJD experience

Slovakia	69,5%
Italy	17,4%
Austria	14,4%
France	9,0%
Canada	8,5%
Germany	7,6%
UK	6,6%
Netherland	2,1%
Switzerland	1,2%
Mean	10,2%

E200K - most frequent and worldwide spread mutation of the prion protein gene

- 1st detected in 1989 (Goldgaber, Goldfarb, Brown et al. Exper. Neurol. 1989)
- Disease specificity demonstrated in 1990 (Goldfarb, Mitrová, Brown, et al. Lancet , 1990)
- Asymptomatic carriers found in 1991 (Goldfarb, Brown, Mitrová et al. Europ.J. Epidemiol. 1991)
- Penetrance of the E200K mutation is uncomplete (59%) (Mitrová and Belay 2002)

In Slovakia the annual incidence of gCJD in years 1975 - 2008 never exceeded 1,66 /1 mill.

In 2009 it significantly (p=0,006) increased to 3,2/1 mill.

Questions :

- What caused this striking increase ?
- Was this increase transitory or permanent ?

GENETIC CJD PATIENTS WITH THE E200K MUTATION
increased annual incidence in 2009 year

Patient	Age at onset	Gender	Duration	M129V	Onset	Exitus age at onset	CJD relative
1. A. Še.*	**55**	**F**	**7**	**MV**	**07.2009**	**12.04.2009**	**father 45**
2. K. Št.	56	F	4	MM	01.2009	17.04.2009	
4. M. La.	64	F	3	MM	03.2009	20.05.2009	
5. M. Pa.*	**60**	**F**	**2**	**MM**	**04.2009**	**22.05.2009**	**onkel 68**
6. A. Va.	68	F	5	MM	01.2009	14.06.2009	
7. J. Da.	53	M	7	MV	02.03.2009	18.07.2009	
8. M. Dar.*	**58**	**F**	**6**	**MM**	**02.2009**	**12.07.2009**	**aunt 65**
9. V. Ku.*	**56**	**F**	**7**	**MM**	**05.2009**	**14.07.2009**	**father 68**
10. M.Kub.	61	F	5	MM	04.2009	04.09.2009	
11. A. Ga.	58	F	7	MM	03.2009	08.09.2009	
12. O.Ma.*	**54**	**F**	**5**	**MV**	**06.2009**	**18.10.2009**	**aunt 59**
13. A. Bu.	61	F	8	MM	02.2009	20.10.2009	
14. Š. Šľ.*	**67**	**M**	**3**	**MM**	**06.09.2009**	**06.11.2009**	**son 42**
15. P. Šo.*	**54**	**M**	**6**	**MV**	**06.2009**	**18.11.2009**	**father 65**
16. J.Csi.	60	M	3	MM	01.10.2009	16.12. 2009	
17. K. Mo.	56	F	4	MM	09.09.2009	23.12.2009	
18. M. Šr.*	**53**	**M**	**31**	**MV**	**02.2009**	**10.10.2011**	**onk 68, aunt 74**

* Patients from families affected with CJD in successive generations

Results (2009)

- The significant increase of gCJD in 2009 year had a transitory character ; in years 2010 and 2011 it considerably decreased (1,88/million and 2,07/million).

- 10 out of 17 gCJD in year 2009 were familial cases, 8 of them (47%) belonged to a 2nd affected generation.

- The mean age difference at CJD onset in patients from different generations was 14.12 years (p= 0,001).

Questions:

- Does analysis of all familial CJD patients confirm the significant generation age difference (and anticipation) observed in 2009?

-Can be the recognized anticipation practicaly utilized in prevention of gCJD ?

- Genetic testing was performed in 234 definite CJD patients and their 426 relatives.

- Age at death and duration of the disease were compared in fCJD from successive generations in all cases since y. 1975 except in y. 2009 (65)

Results

- Mutation E200K was present in 184 patients (67,9%) and 151 (35,5%) relatives.
- The mean age at death was : 62,20 ±7,219 years in the 1st and 50,04±9,52 years in the 2nd generation. The difference 12,16 years was significant (p<0,001).
- The mean duration was 5.75 ±7,52 months in the 1st and 4,41 ± 3,21months in the 2nd generation. The difference 1,34 was not significant (p=0,773).

- Highly significant „generation age difference“ in both evaluated intervals provide evidence of anticipation, i.e. earlier age at onset in successive generations of carriers of E200K.

- Confirmed anticipation has impact in prophylaxis :

  It is decisive for individual (optimal) determination of the age for starting preventive treatment in healthy carriers of the disease - specific mutation.

Doxycycline as candidate for the prevention...

- **Doxycycline treatment in CJD patients :**
  significantly prolonged the clinical stage of the disease (Fincke et al. 2008, Tagliavini et al. 2008),

- **Experimental doxycycline administration before the clinical onset of the disease either :**
  1. prevented the clinical manifestation of the disease (Tremblay et al, 1998, Safar et al. 2005), or
  2. significantly prolonged the preclinical (incubation) period (De Luigi et al.2008)

In summary....

Studies on the gCJD^{E200K} demonstrate :

- **Familial form** represent only 53,6% of genetic patients.
- **Penetrance** of the mutation is uncomplete (59%).
- **Anticipation** (12-15 yrs.) in familial patients, as well as its influence on the annual incidence of the disease.

Obtained data draw attention to the
decisive role of the optimal age when the preventive drug (Doxycycline) administration should be started

and underline as important
to consider in each asymptomatic carrier (individually) :
- the age of youngest affected family member,
- the anticipation.

Many thanks to.....

People involved.....

Department of prion diseases.

Thank you for your attention